Assessment of Head and Neck Squamous Cell Carcinomas in Minority Racial/Ethnic Groups in the US

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THESIS

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Dedicated to all those who have encouraged me to aim higher; to my parents who have been my pillars of strength; to Dr. Arlene Keddie, who first introduced me to Epidemiology and was the first one to encourage me to go for PhD; to my husband and my daughters for their support; and above all, to my Almighty for the spiritual strength that kept me going.

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LIST OF ABBREVIATIONS

ACA	Affordable Care Act
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
EBV	Epstein Barr Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
HR	High-Risk (HPV)
I/P	(Asian) Indian/Pakistani
IARC	International Agency for Research on Cancer
LR	Low-Risk (HPV)
NCDB	National Cancer Database
NCI	National Cancer Institute
NHW	Non-Hispanic White
NHB	Non-Hispanic Black
Non-OPC	Non-Oropharyngeal Cancer
OCC	Oral Cavity Cancer
OPC	Oropharyngeal Cancer
OR	Odds Ratio
PCP	Primary Care Practitioner
SEER	Surveillance, Epidemiology and End Results
SES	Socio-Economic Status
WHO	World Health Organization

SUMMARY

Head and neck squamous cell carcinomas (HNSCCs) comprise 90% of all head and neck cancers (Chi, Day, & Neville, 2015; Vigneswaran & Williams, 2014), which represent the eighth most common cancer in males in the US (Siegel, Miller, & Jemal, 2019; Vigneswaran & Williams, 2014) and the most common cancer in males in parts of Asia (International Agency for Research on Cancer (IARC) GLOBOCAN 2018, 2019; Joshi, Dutta, Chaturvedi, & Nair, 2014; Vigneswaran & Williams, 2014; World Health Organization (WHO), 2008). The focus of this study was to examine male HNSCC cases from minority racial/ethnic groups, with emphasis on three of the largest Asian subpopulations (namely, Chinese, South Asian Indians/Pakistanis (I/P) and Filipinos) in the US and compare them to non-Hispanic Whites (NHW). National Cancer Database (NCDB) was used to analyze racial/ethnic differences in site group, Human Papillomavirus (HPV) status, late stage diagnosis, overall survival and temporal trends. Each of the aims are summarized in the following table.

TABLE

A SUMMARY OF THE THREE AIMS

	AIM 1	**AIM 2**	**AIM 3**
Focus of the study	Examine the differences in site group, HPV status (for oropharyngeal cancers), and temporal trends by race/ethnicity	Examine racial/ethnic differences in site group, late stage diagnosis and temporal trends	Examine racial/ethnic differences in all-cause mortality and overall survival
Sample description (N)	Male HNSCC cases (N=192,327 for main analysis)	Male HNSCC cases (N=159,359 for main analysis)	Male HNSCC cases (N=140,638)
Comparison Groups	All minority racial/ethnic groups compared to NHW	Three largest Asian groups (Chinese, South Asian I/P, Filipino) in the US compared to NHW	Three largest Asian groups (Chinese, South Asian I/P, Filipino) in the US compared to NHW
Data Source (Years)	NCDB (2004-2013 for main analysis, 2009-2013 for HPV analysis)	NCDB (2004 – 2013)	NCDB (2004 – 2012)
Methods used	Multinomial logistic models, Annual Percentage Change for temporal trends	Multinomial logistic models, Annual Percentage Change for temporal trends	Kaplan Meier survival estimates, Log rank test, Cox Proportional Hazards Model
Key Results	Younger age at diagnosis in minority groups, especially in Asians Significant racial/ethnic differences in site group and HPV status Asians had the highest likelihood of certain HNSCCs, including non-oropharyngeal and oral cavity cancers HPV 16/18 positive oropharyngeal cancers were less likely among minority groups The proportion of oral cavity cancers increased tremendously among Asians	Asian subgroups had higher likelihood of diagnosis at a younger age South Asians had a greater proportion of oral cavity cancers, while Chinese and Filipinos had a far greater proportion of non-oropharyngeal cancers South Asians and Filipinos had a lower proportion of HPV 16/18 positive tumors HNSCC cases doubled among South Asian I/P during study period	Overall, all three Asian groups had better survival and lower hazards of dying than NHW Chinese males fared best, overall, in survival consistently over time For oropharyngeal cancers, South Asian I/P had poorer survival than other Asian groups and NHW

I. INTRODUCTION

A. Aims and Hypotheses

The overarching goal of this research was to assess racial/ethnic differences in site group, Human Papillomavirus (HPV) status, stage at diagnosis and overall survival in male head and neck squamous cell carcinoma (HNSCC) cases from minority racial/ethnic groups in the US, with special focus on the largest Asian diasporas, namely, Chinese, South Asian Indians/Pakistanis (I/P), and Filipinos.

1. Specific Aim 1

To examine the differences in distribution of HNSCC site group (oral cavity, oropharynx, non-oropharynx and larynx) and HPV status (HPV 16/18 positive, HPV 16/18 negative and HPV unknown for oropharyngeal cancer) in male HNSCC cases from minority racial/ethnic groups including Asians, Pacific Islanders, American Indians, Hispanics, Non-Hispanic Blacks (NHB) and compare them to Non-Hispanic Whites (NHW) on a national level in the US, and to explore temporal trends by site group and by HPV status (in oropharyngeal cancers (OPC)) among minority racial/ethnic groups. We hypothesized that significant racial/ethnic differences will exist by site group, especially with Asians having higher likelihood of cancers of certain sites that are less common in NHW and other racial/ethnic groups, and by HPV status.

2. Specific Aim 2

To assess differences in site group and stage of cancer among male HNSCC cases from three largest Asian subpopulations in the US and compare them to NHW. Our sub-aim was to explore temporal trends by site group and subsite. We hypothesized that in comparison to NHW,

oral cavity cancer (OCC) will be more common in South Asian I/P while non-oropharyngeal cancer (Non-OPC) will be higher in Chinese mainly due to higher risk of nasopharyngeal cancer as is observed in Asia (Cao, Simons, & Qian, 2011; Warnakulasuriya, S., 2009), and significant differences will exist in stage at diagnosis with Asian subgroups having more advanced stage at diagnosis, potentially due to lack of screening awareness and lack of dental insurance.

3. **Specific Aim 3**

To examine the all-cause mortality and overall survival in male HNSCC cases among three of the largest Asian subgroups in the US and compare them to NHW. Our hypothesis was that racial/ethnic differences in survival and all-cause mortality will exist with some Asian groups having better survival than NHW as has been observed for other cancers (Trinh et al., 2015).

B. Rationale for Proposed Research and its Significance

The purpose of this research was to examine HNSCCs in males of racial/ethnic groups beyond NHW and NHB as these two groups have been the focus of most of the research in this field. Moreover, Pacific Islanders and Asians are two distinct groups that have usually been lumped together in the limited literature available on them. We studied these two groups separately. After examining Asians, we focused on the three largest Asian subpopulations in the US (namely, Chinese, South Asian I/P and Filipino) to understand whether the high rates of specific HNSCC sites observed in Asia (Cao et al., 2011; Warnakulasuriya, 2009) persist in these diasporas in the US, and to determine how these groups, which are the fastest growing subpopulations in the US (Pew Research Center, 2019), are doing in comparison to NHW.

While the trends are known for overall incidence rates of HNSCCs in the US population and in NHW and NHB specifically, not much is known about the trends in other racial/ethnic groups, especially when HNSCCs are broken down by specific site group and by HPV (OPC) status. Some of the minority racial/ethnic groups have distinct risk factors, such as concurrent tobacco and alcohol use in American Indians (Falk, Yi, & Hiller-Sturmhöfel, 2008), areca nut use (Aziz, 2010) and Epstein Barr Virus (EBV) (Xu et al., 2019) in Asians, more specifically in South Asians and Chinese, respectively, which may put them at a higher risk.

It is known that HPV has a propensity for certain sites, such as oropharynx, in head and neck region. In our earlier work (Peterson et al., 2016; Peterson et al., 2017) we have examined HPV positive cancers in NHW and NHB males using National Cancer Database (NCDB), which collects HPV testing information, but rates of both HPV positive and negative cancers for other racial/ethnic groups are still not known at a national level. The pattern seen in NHW and NHB is not likely to be the same in other racial/ethnic groups due to different risk factor profiles.

The incidence of HNSCCs is very high in Asia. Indian subcontinent has one of the highest rates of HNSCCs, mainly OCC (IARC GLOBOCAN 2018, 2019; Warnakulasuriya, 2009), along with poor survival and prognosis. In fact, OCC is the most common type of cancer in males in Indian subcontinent mainly due to the widespread use of areca nut and smokeless tobacco (Joshi et al., 2014; Khan, Tönnies, & Müller, 2014). Similarly, nasopharyngeal cancer risk is high in Chinese (Cao et al., 2011; Jia et al., 2006). These high rates are likely to persist in these Asian diasporas living in the US.

Research from other developed countries shows that as Asians migrate to other parts of the world, high-risk habits persist (Ahluwalia, 2005), and so does their risk of HNSCCs (IARC, 2007; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004;

McCredie, Williams, & Coates, 1999; Moles, Fedele, Speight, Porter, & dos Santos Silva, 2008; Warnakulasuriya, K., Johnson, Linklater, & Bell, 1999; Warnakulasuriya, S., Trivedy, & Peters, 2002). A study done in South Asians in the South East England using data from 1985-1995 found much higher age standardized incidence of OCC (4 per 100,000 in South Asian males vs. 2.3 per 100,000 in Non-South Asian males) and pharyngeal cancer (2.2 per 100,000 South Asian males vs. 1.5 per 100,000 Non-South Asian males). After controlling for age and socioeconomic deprivation, South Asian males were 1.36 (IRR=1.36; 95% CI: 1.11 – 1.67) times more likely to have OCC than Non-South Asian males in England (Moles et al., 2008). Literature on HNSCCs in Asian subpopulations in the US is extremely limited and few studies (Jin, Pinheiro, Xu, & Amei, 2016; Rastogi et al., 2007) that have examined HNSCCs, have done so without keeping HNSCCs as their primary focus. Therefore, HNSCC specific analysis (by site and HPV status) and results were not the focus of those studies.

Asians are the fastest growing minority group in the US (Pew Research Center, 2019). However, the risk of HNSCCs in specific Asian diasporas in the US is unknown. It is important to assess the burden of HNSCCs and characterize the type and clinical picture of HNSCCs in these groups. This study overcomes the current gap in our knowledge of HNSCCs in minority groups. Although these minority groups contribute a smaller percentage of cases than NHW, identifying high risk subgroups within these racial/ethnic groups can be beneficial for targeting early screening and risk factor reduction programs.

C. Rationale for Restricting the Study to Males only

The rates of HNSCCs are much higher in males than females. Overall, males account for two-thirds of all cases but for certain sites in head and neck region and for certain populations, males can be at five to twenty-three times higher risk than females (Shield et al., 2017). In the US specifically, according to Surveillance, Epidemiology, and End Results Program (SEER), males are more than twice as likely to develop HNSCCs as females; however, for oropharyngeal cancer (OPC), in particular, the rate is four times higher in males (Howlader et al., 2019) and for laryngeal cancer, the rate is five times higher in males than females (NCI SEER, n.d.). This difference by sex may be even higher in certain racial groups; for instance, laryngeal cancers are eight times more common in Hispanic males, and seven times more common in Asian/Pacific Islander males, than females (NCI SEER, n.d.).

It is important to study HNSCCs in both sexes; however, we restricted our study to males because of concerns with sample size. When female cases reported to NCDB are broken down into racial/ethnic groups, the sample becomes extremely small, with cell sizes as small as three. Table I provides more detail on the sample size of female HNSCC cases (by race/ethnicity, HPV status and site group) available through NCDB.

TABLE I

SAMPLE SIZE OF FEMALE HNSCC CASES BY RACE/ETHNICITY, HPV STATUS AND SITE GROUP, 2004 - 2013

	Overall	HPV status		Site Group			
	Female HNSCC cases N=71,840 n (%)	Females with HPV 16/18 positive HNSCC N=1,697 n (%)	Females with HPV 16/18 negative HNSCC N=7,002 n (%)	Females with OCC N=31,284 n (%)	Females with OPC N=16,589 n (%)	Females with Non-OPC N=6,794 n (%)	Females with Laryngeal cancer N=17,173 n (%)
NHW	55,018 (76.6%)	1467 (86.4%)	5592 (79.9%)	24774 (79.2%)	13033 (78.6%)	4388 (64.6%)	12823 (74.7%)
NHB	7622 (10.6%)	110 (6.5%)	720 (10.3%)	2383 (7.6%)	1778 (10.7)	1008 (14.8%)	2453 (14.3%)
Hispanic	7059 (9.8%)	89 (5.2%)	464 (6.6%)	3169 (10.1%)	1494 (9.0%)	677 (10.0%)	1719 (10.0%)
American Indian	194 (0.3%)	**4 (0.2%)**	24 (0.3%)	74 (0.2%)	48 (0.3%)	27 (0.4%)	45 (0.3%)
Asian	1839 (2.6%)	26 (1.5%)	197 (2.8%)	835 (2.7%)	218 (1.3%)	663 (9.8%)	123 (0.7%)
Chinese (n)	427	**4**	40	136	23	258	**10**
South Asian I/P (n)	315	**5**	42	213	32	47	23
Filipino (n)	218	**3**	**18**	75	33	92	**18**
Pacific Islander	108 (0.2%)	**1 (0.1%)**	**5 (0.1%)**	49 (0.2%)	**18 (0.1%)**	31 (0.5%)	**10 (0.1%)**

D. Background

1. Overview of HNSCCs

Cancers that originate in the epithelial surfaces in head and neck region are collectively known as head and neck cancers (National Cancer Institute (NCI), 2017). Head and Neck Cancers do not include cancers of brain, thyroid, eyes, skin, muscles and bones (NCI SEER Training Modules, n.d.). As more than 90% of the Head and Neck Cancers develop in squamous cell lining of the mucosa in head and throat area (Chi et al., 2015; Vigneswaran & Williams, 2014), they are commonly referred to as Head and Neck Squamous Cell Carcinomas (HNSCCs).

a. Sites

The sites in head and neck region are-

- Oral cavity which includes lips, anterior tongue (i.e., front two/thirds of the tongue), gums, floor of mouth, hard palate, buccal mucosa (inner lining of the cheek), labial mucosa (inner lining of lips) and retro-molar area (i.e., the area behind the wisdom tooth) (NCI, 2017; NCI SEER Training Modules, n.d.).
- Pharynx which includes nasopharynx (i.e., upper part of pharynx that lies posterior to the nasal cavity), oropharynx (i.e., middle part of pharynx that lies behind oral cavity, and also includes base (or posterior one/third) of tongue and tonsils) and hypopharynx (i.e., lower part of pharynx) (NCI, 2017; NCI SEER Training Modules, n.d.).
- Larynx which is an apparatus in the neck that holds the vocal cords and protects the entryway of the lower respiratory passage (NCI, 2017; NCI SEER Training Modules, n.d.).
- Paranasal Sinuses and nasal cavity which include the lining of the sinuses that surround the nasal cavity and the lining of nasal cavity (NCI, 2017; NCI SEER Training Modules, n.d.).

Salivary gland tumors are typically not squamous cell carcinomas owing to the diversity of cells that constitute salivary glands (Boukheris, Curtis, Land, & Dores, 2009; NCI, 2017) and have different etiology than rest of the head and neck cancers. They are also rare. As this study was limited to squamous cell carcinomas, salivary gland tumors were excluded (Boukheris et al., 2009; Peterson et al., 2016).

b. **Causes of HNSCCs**

Each of the risk factors for HNSCCs carry different risk for different anatomic sites within head and neck region (Applebaum et al., 2007; Smith, Rubenstein, Haugen, Pawlita, & Turek, 2012). While World Health Organization (WHO) estimated that 90% of all oral cancers can be attributed to tobacco and heavy alcohol use (WHO, 2005), Hashibe et al (2009) found that 74% of head and neck cancers in males (72%, overall, for both sexes) were attributable to tobacco and alcohol use (based on European and American case-control studies) (Hashibe et al., 2009).

1) **Tobacco**

Apart from being associated with several oral conditions like periodontal disease, recession of gums and premalignant lesions such as leukoplakia, tobacco is a major risk factor for HNSCCs (Winn, 2001). The risk of developing HNSCCs increases as the amount and duration of use increases but the risk decreases after tobacco use is discontinued and continues to drop as the duration since quitting tobacco increases (Winn, 2001).

- Tobacco Smoking, which includes tobacco smoked in any form, be it cigarette, cigar, pipe, *bidi* (hand rolled cigarette made of unprocessed tobacco, very common in India but are also available in other parts of the world including the US (American Cancer Society, 2019)),

kretek (cigarette containing cloves and other flavorings besides tobacco (American Cancer Society, 2019)) or *hookah/shisha* (water pipe used for smoking tobacco (American Cancer Society, 2019)), is associated with higher risk of HNSCCs (Amtha et al., 2014; Mamtani et al., 2017; Rahman, Sakamoto, & Fukui, 2003; Winn, 2001; Wyss et al., 2013). In a pooled analysis, Wyss et al (2013) found ever smokers to have three times (OR=3.4; 95% CI: 3.1 – 3.6) higher odds of having HNSCCs than never smokers (Wyss et al., 2013). A significant dose response relationship exists with the number of cigarettes smoked, and the duration of smoking in years and pack-years (Castellsagué et al., 2004; Wyss et al., 2013)

Quitting smoking reduces risk significantly but takes a long time to get to the level of non-smokers (Castellsagué et al., 2004; Winn, 2001). In a study conducted by Castellsagué et al (2004), the oral cancer risk among ex-smokers came close to that of non-smokers nearly 17 years after smoking cessation. Smoking cigarettes with or without filter does not make a difference in risk. The age at which smoking is initiated or is quit has no effect after controlling for duration of smoking (Castellsagué et al., 2004). Smoking is the strongest risk factor for laryngeal cancer (Applebaum et al., 2007). It is also associated with worse outcomes and poorer prognosis, independent of the type of treatment (Gillison, Zhang et al., 2012; Osazuwa-Peters, Boakye, Chen, Tobo, & Varvares, 2018) and p16 (a diagnostic marker) status of the tumor (Gillison et al., 2012). The risk of tumor progression and mortality is higher if the patient smokes during treatment (Gillison et al., 2012).

- Smokeless Tobacco, i.e. tobacco consumed without burning, can be used orally (by chewing or by sucking, also known as dipping, on tobacco preparations placed in the mouth) or nasally (by sniffing) (WHO SEARO, 2004). Smokeless tobacco contains at least 28 different carcinogens (IARC, 2007) and is an independent risk factor for HNSCCs, mainly cancers of

oral cavity (IARC, 2007; Winn et al., 1981). It is typically placed in between the gums and cheeks or lips (IARC, 2007), and the risk tends to be manifold higher for the sites that come in direct contact with tobacco (Winn et al., 1981). The risk is higher for chewing tobacco (summary OR=4.4; 95% CI: 3.3 - 5.8) than the non-chewing tobacco preparations (Asthana, Labani, Kailash, Sinha, & Mehrotra, 2018). Smokeless tobacco use is extremely common in some countries, such as countries in South-East Asia including India (WHO SEARO, 2004), where OCC is among the most common cancers in males (IARC GLOBOCAN 2018, 2019). Ninety percent of the global smokeless tobacco users live in South-East Asia (WHO SEARO, 2013) and the use continues to be high in the immigrants from this region settled elsewhere (IARC, 2007; WHO SEARO, 2004). The type of tobacco preparation varies by geographic region. *Khaini*, i.e. a preparation of tobacco with lime, with or without additional constituents, is one of the common forms of smokeless tobacco used in South-East Asia, while (moist or dry) snuff is used in Europe and the US (IARC, 2007).

2) **Alcohol**

All types of alcoholic beverages have been associated with HNSCCs; however, spirit drinks carry the most risk potentially owing to the high ethanol content (Castellsagué et al., 2004). Heavy drinking is a strong risk factor for HNSCCs that also exhibits a dose response pattern (Goldstein, Chang, Hashibe, La Vecchia, & Zhang, 2010) but some studies suggest that even light drinking increases the risk. While Castellsagué et al (2004) found an increase in oral cancer (i.e., oral cavity and pharyngeal cancer) risk with even one drink a day (Castellsagué et al., 2004), Rao & Desai (1998) found an increase in risk of cancer of base of tongue with even once per day drinking habit (Rao & Desai, 1998). Out of all HNSCCs, the risk is highest for OCC, followed by pharyngeal cancer (Applebaum et al., 2007). There is variation

in the magnitude of association reported across studies, with estimates in the range of two to 14, and three to 12 have been reported for OCC and pharyngeal cancer (including OPC), respectively in heavy drinkers (Goldstein et al., 2010). The risk decreases after three years of quitting drinking but may take over 14 years (Castellsagué et al., 2004) or more (Hayes et al., 1999) to bring the risk down to the level of teetotaler. Like tobacco, age at the time of initiation of drinking or the age at quitting does not have a significant impact after controlling for duration (Castellsagué et al., 2004).

The joint effect of tobacco and alcohol is more than multiplicative (Castellsagué et al., 2004; Goldstein et al., 2010; Hashibe et al., 2009; Hayes et al., 1999). This synergistic effect can result in 13 times (OR=12.7; 95% CI: 5.5 – 29.1) elevated risk in people who drink and smoke concurrently (Castellsagué et al., 2004). Among heavy smokers and heavy alcohol users, the joint effects can lead to 40 to 50 times higher risk than non-users (Castellsagué et al., 2004; Hayes et al., 1999).

3) **Areca Nut**

Areca nut, also commonly referred to as betel nut, is widely consumed in Asia-Pacific region including Indian subcontinent (India, Pakistan, Bangladesh and Sri Lanka), Melanesia and China, and in other countries where Asian migrant communities exist (Gupta & Warnakulasuriya, 2002; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). Areca nut use has been reported in migrant populations in North America, Europe and Australia (Gupta & Ray, 2004; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004; Joshi et al., 2014). Nearly 10 percent of the global

population consumes areca nut regularly; the largest consumption being in India (Gupta & Warnakulasuriya, 2002).

Areca nut is used as a stimulant and a digestive aide (Aziz, 2010; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). It is usually wrapped in a betel leaf (together called betel quid) with sweeteners, catechu and flavors, with or without tobacco (Gupta & Warnakulasuriya, 2002). Even though areca nut chewing is a major independent risk factor for HNSCCs, mainly OCC (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004), betel nut or betel quid is widely consumed and is culturally acceptable in Indian subcontinent. In fact, it is considered a part of sociocultural practices, religious activities and traditional medicine (Aziz, 2010; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004). Migration contributes to the spread of betel nut chewing habit to western countries, including the US (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004; Warnakulasuriya et al., 2002). When areca nut is combined with tobacco and alcohol, the risk becomes even higher (Lin, W., Jiang, Wu, Chen, & Liu, 2011). Substitutes of betel quid (namely *pan masala*, i.e. areca-nut packaged in small sachets for individual use, and *gutka*, i.e. areca nut packaged with tobacco in small sachets for individual use) are also used in Asian countries as well as by Asian migrants (Gupta & Warnakulasuriya, 2002; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004; Warnakulasuriya et al., 2002). The users of these preparations develop red or white lesions in mouth or develop oral sub-mucous fibrosis (stiffening of oral mucosa due to formation of sub-mucous fibrous bands) (Gupta & Ray, 2004; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004; Joshi et al., 2014; Nair, Bartsch, & Nair, 2004). Nearly two to 12% of these precancerous lesions turn malignant (Nair et al., 2004).

4) **Human Papillomavirus**

Human Papillomavirus (HPV) belongs to a family of DNA viruses that cause infection of the skin and the mucous membranes (Longworth & Laimins, 2004; Psyrri & DiMaio, 2008). There are more than 200 different types of HPVs (Psyrri & DiMaio, 2008), some referred to as low-risk and some as high-risk types (Longworth & Laimins, 2004; Psyrri & DiMaio, 2008). Infection by HPV is the most common sexually transmitted infection and almost every unvaccinated sexually active person will acquire it during their lifetime through intimate skin to skin contact or sexual contact that includes vaginal, anal or oral sex. According to Centers for Disease Control and Prevention (CDC), the infection is mostly self-limiting and presents no signs and symptoms (CDC, 2017a). In 2009 - 2010, almost seven percent of the US population (between 14 to 69 years of age) had an oral HPV infection, and one percent had HPV 16 oral infection. The rates of infection are higher in males (10 percent) than females (four percent) (Gillison, Broutian et al., 2012).

Human Papillomavirus is responsible for 70 percent of all OPCs in the US (Chaturvedi et al., 2011) and HPV 16 is considered an independent risk factor for HPV-related HNSCCs, mainly OPC (D'Souza et al., 2007; Gillison, 2004; Gillison et al., 2008). It accounts for 90 percent of HPV-related OPCs (Kreimer, Clifford, Boyle, & Franceschi, 2005; Lowy & Munger, 2010; Psyrri & DiMaio, 2008), which is the second most common cancer caused by HPV after cervical cancer (Viens, 2016). Besides HPV 16, HPV 18 is another high-risk type associated with OPCs and other HNSCCs (Kobayashi et al., 2018; Kreimer et al., 2005).

Head and neck cancers in young, male, non-smoker patients have been attributed to HPV (Chaturvedi, Engels, Anderson, & Gillison, 2008; Chaturvedi et al., 2011; Gillison, 2007), which

are now becoming number one cause of HNSCCs in younger age group. Infection with HPV 16 increases the odds of HNSCC development by 14 times (some studies report 30 times higher risk of pharyngeal cancer among non-smokers and among light drinkers (Applebaum et al., 2007)), when compared to those not infected (D'Souza et al., 2007). There is no clear evidence whether HPV has synergistic effects with tobacco or alcohol; where some studies have reported such an effect (Smith et al., 2004), other have not found any synergy (D'Souza et al., 2007; Gillison et al., 2008).

Interestingly, HPV-associated OPC is distinct from other types of HNSCCs because of its etiology, pathogenesis, clinical features and prognosis (Gillison, 2004; Gillison et al., 2008; Lowy & Munger, 2010). Therefore, HNSCCs can be broadly categorized as HPV-related (positive for high risk type HPV 16 or 18 or both) and HPV-unrelated (negative for HPV 16 and 18, so are likely to be caused by tobacco, alcohol or betel quid use). The HPV-related HNSCCs are more likely to be seen in white males who are non-smoker and non-drinker (Chaturvedi et al., 2008; Cleveland et al., 2011; Gillison et al., 2000). They are more likely to occur at a younger age (30 to 50 years compared to 50 to 70 years in HPV-unrelated HNSCCs (Martín-Hernán, Sánchez-Hernández, Cano, Campo, & del Romero, 2013)), diagnosed at an advanced stage but have a better chance of survival (Chaturvedi et al., 2008) (59 percent lower risk of dying after controlling for heavy alcohol consumption (Gillison et al., 2000)) and lower chance of recurring than HPV-unrelated HNSCCs (Rettig & D'Souza, 2015). They are also less likely to have TP53 mutations (Gillison et al., 2000), less likely to metastasize to distant sites (Martín-Hernán et al., 2013) and respond better to radiation and chemotherapy (Cleveland et al., 2011).

5) **Epstein Barr Virus**

Epstein Barr Virus (EBV) is a risk factor for nasopharyngeal cancer, particularly the undifferentiated form of nasopharyngeal cancer (Young & Dawson, 2014). Two variants of EBV have been found to have a strong association with nasopharyngeal cancer (ORs in the range of 6.1 and 8.7), accounting for 83% of the risk in Southern region of China (Xu et al., 2019).

6) **Diet**

Fruits, vegetables and lean protein have been found to have a protective effect, with reduced odds of having oral/pharyngeal cancers as well as laryngeal cancers (Bradshaw et al., 2012). Fried foods, processed meats and sweets have been found to be associated with increased odds of having laryngeal cancers but not with oral/pharyngeal cancers (Bradshaw et al., 2012). Franceshi et al also found vegetables and fruits to have protective effect but among fruits, only citrus fruits (OR=0.5; 95% CI: 0.3 - 0.7 in the highest intake quintile) were found to have a significant protective effect, while high intake of butter (OR=2.3; 95% CI: 1.6 - 3.5 in the highest intake quintile) was found to be a significant risk factor (Franceschi et al., 1999).

Cantonese diet, such as salted fish and preserved/cured foods have been linked to nasopharyngeal cancer. Jia et al. (2010) found the risk to be higher for consumption of these Cantonese foods, irrespective of whether they were consumed during adulthood or childhood. In those that consumed salted fish and preserved/cured meat at least weekly during childhood, the OR was as high as 2.4 (95% CI: 2.0 – 2.9) and 2.1 (95% CI: 1.2 – 3.6), respectively. High nitrosamine content is thought to be the reason for the increased risk (Jia et al., 2010).

7) **Other Risk Factors**

Occupational exposures such as asbestos (De Stefani et al., 1998) and wood dust (Mimi & Yuan, 2002), family history (Anaya-Saavedra et al., 2008; Foulkes, Brunet, Kowalski, Narod, & Franco, 1995), lack of oral hygiene (Mathur, Singhavi, Malik, Nair, & Chaturvedi, 2019) and maté drinking (a tea-like beverage, typically consumed very hot, widely consumed in South America and in other parts of the world (Dasanayake, Silverman, & Warnakulasuriya, 2010; De Stefani et al., 1987; Goldenberg, Golz, & Joachims, 2003; Loomis et al., 2016); summary OR=2.1; 95% CI: 1.4 – 3.2 for the association of maté with oral and oral-pharyngeal cancers (Dasanayake et al., 2010)) are some other risk factors. Sun exposure is a risk factor for lip cancers (Vigneswaran & Williams, 2014).

c. **Signs and Symptoms of HNSCCs**

The signs and symptoms may include occurrence of white patches (i.e., leukoplakia) or red patches (i.e., erythroplakia) in the mouth (Vigneswaran & Williams, 2014), a mouth sore that does not heal and bleeds easily, loosening of teeth, feeling a lump or a mass in the neck or cheek, pain or difficulty in swallowing, sore throat, pain in the ear, hoarseness or change of voice (McIlwain, Sood, Nguyen, & Day, 2014) trouble in chewing, difficult movement of jaws and/or tongue, numbness and a swelling in the jaw (NCI, 2017).

2. **Descriptive Epidemiology**

a. **Global Epidemiology**

Head and neck cancers are the sixth most common type of cancers in the world (Warnakulasuriya, 2009), accounting for 4.6% of all cancer cases and 4.5% of all cancer deaths

in 2018 (Bray et al., 2018). For males specifically, the global age-standardized incidence rate for the cancers of oral cavity (including lip), oropharynx, nasopharynx and hypopharynx was 5.8, 1.8, 2.2 and 1.6 per 100,000, respectively in 2018 (Bray et al., 2018). More than 800,000 cases of HNSCCs were diagnosed globally in 2018 (Bray et al., 2018). Worldwide, the incidence of HNSCCs is projected to increase by 62% by year 2035 (Shield et al., 2017). This increase is expected mainly due to population growth and population aging (Shield et al., 2017); in the developed countries, the increase is expected primarily due to a rise in HPV related cancers (Chaturvedi et al., 2011).

Head and neck cancers are much more common in males than females. Globally, approximately three-fourths of the new diagnoses per year are in males (Bray et al., 2018; Shield et al., 2017). For OCC, the ratio of male to female is more than 2:1 (Bray et al., 2018), with certain geographic areas having a ratio higher than 5:1 (Shield et al., 2017). For OPC, this ratio is more than 4:1 (Bray et al., 2018), with certain areas having a ratio higher than 7:1 (Shield et al., 2017). For hypo-pharyngeal cancers the male to female ratio is 5:1 (Bray et al., 2018; Shield et al., 2017) but can be as high as 23:1 in certain areas (Shield et al., 2017).

There is substantial variation in incidence, overall and by anatomic site and HPV status, across geographic areas (Bray et al., 2018; Shield et al., 2017; Vigneswaran & Williams, 2014), with HNSCCs being the most common type of cancers in developing countries, which include parts of South and South-East Asia (Joshi et al., 2014; Vigneswaran & Williams, 2014; WHO, 2008) that includes India, Pakistan, Sri Lanka and Bangladesh where OCC is the most prevalent cancer in men (Bhurgri et al., 2006; Joshi et al., 2014; Vigneswaran & Williams, 2014). In the developed world, the incidence and mortality from HNSCCs is lower. In North America and Europe, HNSCCs contribute five to ten percent of all cancer cases (Vigneswaran & Williams,

2014). Where OPCs are more common in North America and Europe; OCCs are highly prevalent in South Asia (Bhurgri et al., 2006; Shield et al., 2017), and nasopharyngeal cancer is most common in East/Southeast Asia, including China (Shield et al., 2017). The risk for hypopharyngeal cancer is also highest in South Asian countries of Bangladesh and Sri Lanka (Shield et al., 2017). These regional variations are largely due to variations in prevalence of risk factors, where smokeless tobacco and areca nut use drives the higher risk of OCC in South Asia (Joshi et al., 2014; Khan et al., 2014), changing sexual practices are perhaps driving the increase in HPV related OPC in North America (Chaturvedi et al., 2008). Other reasons that may lead to higher prevalence of cancers of certain sites are the variations in diagnostic work-up, treatment and survival (Shield et al., 2017).

b. **Epidemiology in the United States**

In the US, head and neck cancers account for almost four percent (3% for oral and pharyngeal and 0.7% for laryngeal cancers) of all new cancer cases and more than two percent of all cancer deaths (NCI SEER, n.d.) and are the eighth most common cancer in males (Siegel et al., 2019; Vigneswaran & Williams, 2014). In 2019, nearly 65,410 new cases (53,000 for oral/pharyngeal and 12,410 for laryngeal) and 14,620 deaths (10,860 for oral/pharyngeal and 3,760 for laryngeal) were estimated to occur due to HNSCCs in the US. The incidence rate in males is 22.2 per100,000 (calculated from SEER incidence reported for oral and pharyngeal cancers, i.e. 17 per 100,000, and laryngeal cancers, i.e. 5.2 per 100,000) (NCI SEER, n.d.). Despite a decrease in tobacco use, certain HNSCCs have been increasing on an average of 0.8 percent each year for the past decade (NCI SEER, n.d.). Overall, the incidence of OCC and laryngeal cancer has been decreasing, which can be attributed to decrease in tobacco use (Vigneswaran & Williams, 2014) in the US; however, the incidence of OPC has been increasing

due to rise in HPV related HNSCCs (Chaturvedi et al., 2011). While HPV positive OPCs increased by 225 percent from 1988 to 2004, the HPV negative OPCs decreased by 50 percent during the same period (Chaturvedi et al., 2011). The increase in the incidence of OPC is mainly seen in white men (Simard, Torre, & Jemal, 2014).

Based on Surveillance, Epidemiology, and End Results Program (SEER) 2012-2016, the age-adjusted incidence of oral and pharyngeal cancers, combined, in males is highest in Whites, followed by Blacks, American Indians/Alaskan Natives, Asian/Pacific Islanders and Hispanics with rates of 17.9, 13.4, 11.8, 11.8 and 10.1 per 100,000 per year, respectively. The overall age-adjusted mortality rate of oral and pharyngeal cancers, combined, in males is highest in Blacks, followed by Whites, American Indians/Alaskan Natives, Asian/Pacific Islander and Hispanic with mortality rates of 4.7, 3.8, 3.7, 3.1 and 2.4 per 100,000 per year, respectively. For laryngeal cancers, the incidence is highest among Black males, followed by White, Hispanic, American Indian/Alaskan Native and Asian/Pacific Islander males with rates of 7.6, 5.2, 4.2, 3.6 and 2 per 100,000 (NCI SEER, n.d.). However, we do not know what proportion of these cancers, whether oral and pharyngeal, combined, or laryngeal cancers, are HPV positive. Estimation methods using site and cancer cell type more likely associated with HPV have estimated the risk of HPV-attributable OPC to be higher in White males (9 per 100,000 in 2015) than Black males (6 per 100,000 in 2015) and other racial/ethnic groups (Van Dyne et al., 2018). While 65.3% of the oral and pharyngeal cancer cases survive for five years, only 60.3% of laryngeal cancer cases survive for five years (NCI SEER, n.d.).

In the US, HNSCCs are mostly diagnosed in the age group of 55-64 years. The median age at diagnosis is 63 for oral and pharyngeal cancers, combined, and 65 for laryngeal cancer (NCI SEER, n.d.) but HPV related cancers tend to be diagnosed at a younger age (Chaturvedi et

al., 2008). The mortality from HNSCCs is higher than that from cancers like cervical cancer, thyroid and skin cancer (NCI SEER, n.d.). Moreover, survival also varies by HPV status and site of cancer. Cases with HPV related cancers tend to have better survival (Chaturvedi et al., 2008; Gillison et al., 2000) than cases with HPV unrelated cancers with 82 percent HPV positive OPC patients surviving for three years compared to 57 percent in smoking related (HPV negative) OPCs, after adjusting for age, race and stage (Ang et al., 2010).

II. DATA SOURCE

A. National Cancer Database

National Cancer Database (NCDB) is a large nationwide clinical oncology database that collects information on nearly all types of cancers. It was started in 1989 as jointly sponsored project by the American College of Surgeons and the American Cancer Society (American Cancer Society, n.d.; Bilimoria, Stewart, Winchester, & Ko, 2008). The American Cancer Society headquarters in Chicago IL also house the NCDB (Bilimoria et al., 2008). The database collects hospital cancer registry data from over 1500 Commission on Cancer (CoC) accredited facilities (American Cancer Society, n.d.) in the US and Puerto Rico (Bilimoria et al, 2008), which include teaching and research hospitals, comprehensive community cancer centers and community cancer centers (Bilimoria et al., 2008). The database collects information on over 70 percent of all the new cancer cases nationwide (American Cancer Society, n.d.) and has more than 34 million records of cancer cases (American Cancer Society, n.d.; Boffa et al., 2017), which is almost four times the number of records in Surveillance, Epidemiology, and End Results (SEER) (Boffa et al., 2017) database. As a result, NCDB is considered to be the largest clinical registry worldwide (Bilimoria et al., 2008; Boffa et al., 2017).

Only the patients who receive some cancer related care at a CoC accredited facility are reported to NCDB (Boffa et al., 2017). Data are collected from these accredited cancer program registries and submitted to the NCDB using standardized data and coding definitions. Data submitted by CoC hospitals are abstracted from patient medical charts by Certified Tumor Registrars and it undergoes rigorous quality assurance measures. The records that do not meet

the standards are sent back to the hospital. Duplicate cases are identified with a computer algorithm (Boffa et al., 2017).

The database collects information on patient characteristics, including insurance and comorbidity information, tumor characteristics, staging of cancer, histological characteristics of cancer, treatment type and outcomes such as readmission within 30 days, and survival. In addition to these, area level socio-economic status, that includes area level education, area level income and urban/rural residence, and estimation of distance to the CoC hospital are also available through linkage with tertiary data sources such as US Census and US Department of Agriculture (Boffa et al., 2017).

B. **Differences between NCDB and SEER**

A key difference between SEER and NCDB is that since SEER is a population-based registry, the inclusion is based on geographic location; whereas in NCDB the inclusion is based on facility characteristics as the reporting facility has to be CoC accredited. However, SEER captures only 30 percent of the newly diagnosed cancer cases in the US, as opposed to 70 percent (which comes from 30 percent of the 5000 hospitals in the US) in NCDB (Boffa et al., 2017; Mohanty & Bilimoria, 2014). Since NCDB has four times more cases than SEER, it is better in studying subpopulations that have relatively small number of cases. However, the states in SEER are chosen strategically so that they are representative of entire US population (Boffa et al., 2017). On the other hand, the number of cases captured in NCDB varies by the market share of the CoC accredited hospitals in each area; therefore, there may be disparities in representation of some areas (for instance, 89% of the cases are captured in Delaware in contrast to 27% in

Arizona (Lerro, Robbins, Phillips, & Stewart, 2013)) and certain sociodemographic groups in NCDB, which may affect the generalizability of the results.

Results obtained from SEER and NCDB are similar when looking at the overall population but may vary when specific socio-demographic groups are studied (Boffa et al, 2017). Even though the two datasets are dissimilar in terms of sampling cancer cases, Janz et al. found their data to be quite similar in demographics, treatment and survival (Janz et al., 2019). However, certain differences exist in terms of variables and data fields. While NCDB includes information on severity of comorbidities (reported as Charlson/Deyo comorbidity score), type of facility and distance from hospital, SEER does not. Moreover, HPV related information is included in NCDB but for SEER, this information is only available 2013 onwards (Janz et al., 2019). Neither SEER (except SEER-Medicare, which has incomplete data on behavioral factors (NCI, 2019)) nor NCDB collect information on tobacco or alcohol use, which is a significant limitation (CDC, 2012).

III. HEAD AND NECK SQUAMOUS CELL CARCINOMAS IN MALES OF MINORITY RACIAL/ETHNIC GROUPS IN THE US, 2004 - 2013

A. Introduction

In the US, HNSCCs are the eighth most common cancer in males (Siegel et al., 2019; Vigneswaran & Williams, 2014). Certain racial/ethnic differences in risk are known. According to SEER, the incidence of oral and pharyngeal cancers, combined, in males is highest in Whites followed by Blacks, and is lowest in Hispanics. The incidence of laryngeal cancers in males is highest in Blacks followed by White and is lowest in Asian/Pacific Islanders (NCI SEER, n.d.).

Since certain risk factors are associated with specific sites (such as, areca nut and OCC (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004)) within head and neck region and the distribution of risk factors varies by race/ethnicity, it is important to examine racial/ethnic differences by specific sites separately. Oral and pharyngeal cancers are often combined in the literature and presented together which masks the differences by site. Certain minority racial/ethnic groups have distinct risk factors. For example, areca nut use among Asians, mainly South Asians, as has been noticed in South Asians living in the UK and South Africa (Auluck, Hislop, Poh, Zhang, & Rosin, 2009; Gupta & Ray, 2004) is likely to be a problem in the US as well (Aziz, 2010). Smoking and concurrent smoking/drinking in American Indians/Alaskan Natives (Falk et al., 2008) may put them at a higher risk of HPV negative HNSCCs of particular sites instead of HPV-associated OPC, which is more common in NHW. From studies conducted in other developed countries, we know that Asian diasporas tend to be at higher risk of nasopharyngeal cancer and OCC (Kim, Liu, Moghaddamjou, & Cheung, 2014; Moles et al., 2008). Moreover, Asians and Pacific Islanders have been lumped together in the literature. However, these groups are heterogeneous and should be studied separately. Studies

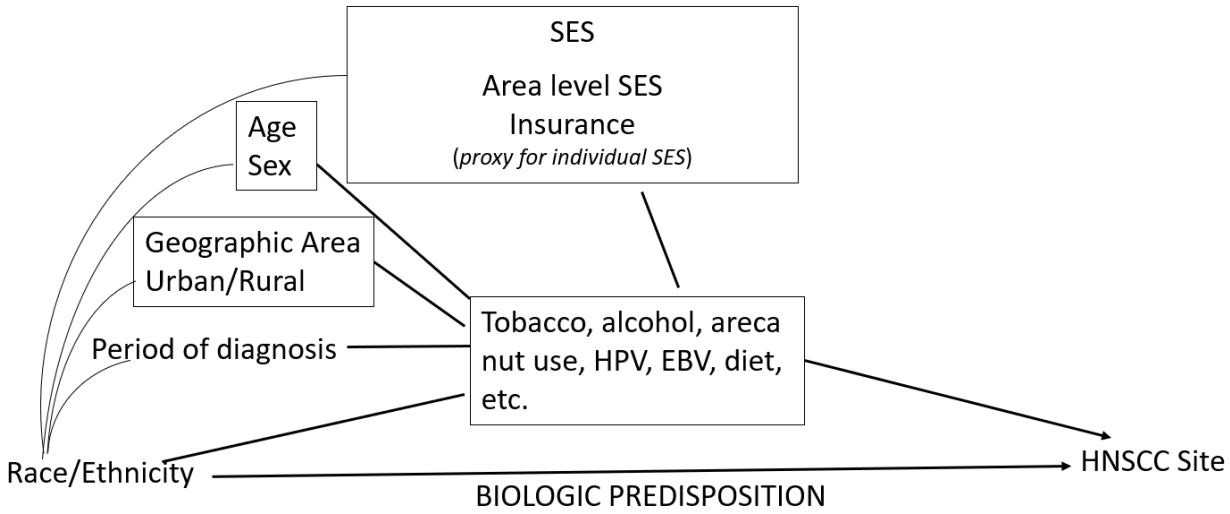
that have examined HPV status by race/ethnicity have mainly focused on Whites and Blacks. Therefore, limited information is available on HPV in OPC cases among other racial/ethnic groups. The few studies that have examined HNSCCs in Hispanics have not included HPV in the analysis (Oh et al., 2017; Parasher et al., 2014).

The purpose of this study was to examine the distribution of HNSCCs by site group and HPV status (among OPC cases) in males of minority racial/ethnic groups including Asians, American Indians, Hispanics, NHBs and compare them to NHWs on a national level in the US. We also assessed the temporal trends in these racial/ethnic subgroups and examined the factors that contributed to the differences. The assessment of relative burden of HNSCCs by site group and HPV status (among OPCs) in these minority racial/ethnic groups may help us in identifying high risk subgroups and high-risk sites. We hypothesized that the distribution of site groups will differ significantly by race/ethnicity and that minority groups will be less likely to have HPV positive OPCs compared to NHW; specifically, Asians and American Indians will be more likely to have HPV negative OPCs, potentially due to differences in sexual behaviors (Choi et al., 2020) and to some extent due to presence of other risk factors, such as high tobacco/alcohol consumption among American Indians. The likelihood of HPV positive HNSCCs will be higher in NHW potentially due to differences in sexual practices.

We developed a conceptual framework (Figure 1) to guide the analysis and to help us identify the potential confounders for the race/ethnicity and site group association. Race/ethnicity is likely to be a predictor of HNSCC site group, both because of biologic reasons (such as genetic predisposition) as well as risk factor differences. Socio-economic status (SES) and insurance are likely to be confounders as they are associated with both race/ethnicity and HNSCC risk. Risk factors such as HPV infection, tobacco, alcohol, areca nut use, diet and EBV

are likely to be confounders as well but except for HPV, we do not have information about the other risk factors, so we could not control for them.

Figure 1: Conceptual Framework for the association of race/ethnicity with HNSCC site group



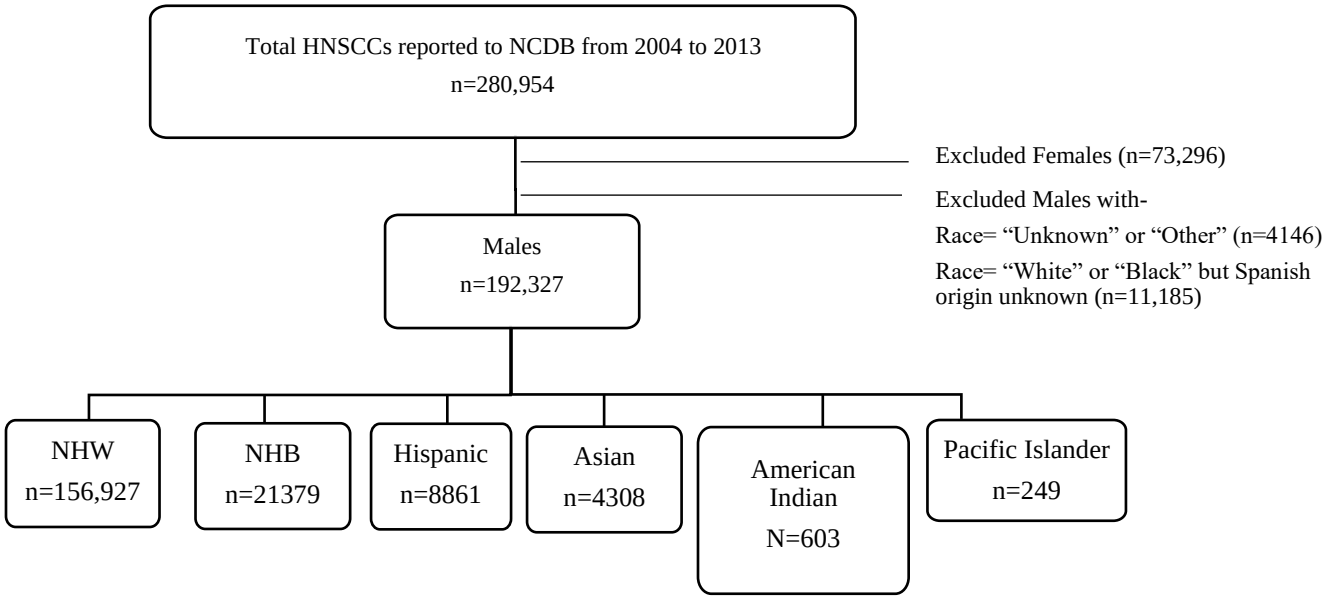
B. Methods

1. Study Population

Male HNSCC cases reported to NCDB from 2004 to 2013 were included in this study. Figure 2 shows the flow chart of the sample size used for the main analysis. The analytic cohort for the main analysis focusing on site group consisted of 192,327 males of NHW, NHB,

Hispanic, American Indian, Asian, and Pacific Islander racial/ethnic groups. However, the analytic cohort for HPV related analysis (not shown in Figure 2) included 39556 cases only because the data was restricted to OPCs diagnosed between 2009 to 2013. Very few cases of HPV positive cancer (1 case in 2006 and 2 cases in 2008) were reported prior to 2009 as HPV testing was not commonly done until late 2000s and routine reporting of HPV status in NCDB began only in 2010 and since the testing is more commonly done and is recommended for OPCs only, we excluded 152771 cases that were diagnosed prior to 2009 and those that were not OPCs. Pacific Islander group could only be included in the preliminary HPV analysis because of its small sample size (i.e., eight HPV 16/18 positive cases and four HPV16/18 negative cases).

Figure 2: Flowchart of the primary analytic cohort used for the main analysis.



2. **Variables**

The main exposure variable was self-identified race/ethnicity, categorized as NHW, NHB, Hispanic, American Indian, Asian, and Pacific Islander. Table II shows the subgroups included in each of these racial/ethnic groups. It is important to note here that to keep the racial/ethnic groups mutually exclusive in the analysis, Hispanic group was restricted to White and Black Hispanics only. Pacific Islanders were studied separately from Asians (Asian Pacific Institute on Gender-Based Violence, n.d.; Friedlaender et al., 2008; Wu Anna & Stram Daniel, 2016) as they are a distinct group of islanders that are different from mainland Asians.

TABLE II

SUBGROUPS INCLUDED IN EACH OF THE RACIAL/ETHNIC GROUPS

Race/Ethnicity	Self-identified Race	Self-identified Hispanic Origin/Ethnicity
NHW	"White"	"Non-Spanish; non-Hispanic"
NHB	"Black"	"Non-Spanish; non-Hispanic"
Hispanic[a]	"White" or "Black"	"Mexican/Chicano", "Puerto Rican", "Cuban", "South or Central America", "Other specified Spanish/Hispanic origin", "Spanish/NOS Hispanic, NOS Latino, NOS", "Spanish surname only" (the surname or maiden name was the only evidence of person's Hispanic origin but no evidence showing the person to be not Hispanic), or "Dominican Republic"
Asian	"Chinese", "Japanese", "Filipino", "Korean", "Vietnamese", "Laotian", "Hmong", "Kampuchean", "Thai", "Asian Indian or Pakistani", "Asian Indian", "Pakistani" or "Other Asian, including Asian, NOS and Oriental, NOS"	
American Indian	"American Indian, Aleutian, or Eskimo"	
Pacific Islander	"Hawaiian", "Micronesian, NOS", "Chamorran", "Guamanian, NOS", "Polynesian, NOS", "Tahitian", "Samoan", "Tongan", "Melanesian, NOS", "Fiji Islander", "New Guinean" or "Pacific Islander, NOS"	

[a]Includes White and Black Hispanics Only.

a. **Outcome Variables**

Two outcome variables studied in this analysis were site group and HPV status. The site groups were categorized as oral cavity, oropharynx, non-oropharynx (Peterson et al., 2016) and larynx. Oral Cavity includes lips, anterior tongue, gums, buccal mucosa, hard palate, and other mouth; oropharynx includes base of tongue and tonsils besides oropharynx; non-oropharynx includes nasopharynx, hypopharynx and other pharynx (Peterson et al., 2016; Piccirillo, Costas, & Reichman, 2007).

We classified HPV status as HPV 16/18 positive (i.e., positive for HPV 16 or HPV 18 or both), HPV 16/18 negative (negative for both HPV 16 and 18 but could be positive for HPV types other than 16/18) and HPV unknown (includes “Not applicable: Information not collected for this case”, “Test ordered, results not in chart”, “Test not done (test was not ordered and was not performed), including no pathologic specimen available for HPV testing”, “Unknown or no information”) ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.). Although a large proportion of cases are likely to have unknown HPV status, given that recommendations for HPV testing of tumors have come into effect only recently for OPCs, it would still be important to examine cases with unknown HPV status. To further explore HPV status comprehensively, we also classified HPV status as HPV 16/18 positive, HPV other High Risk (HR) positive (i.e., HR type other than 16 and 18), HPV Low Risk (LR) positive, HPV (all) negative, and HPV unknown.

For the sub-analysis, HPV status was also categorized as Unknown HPV status (same as HPV unknown) and Known HPV status (positive or negative for any HPV type).

b. **Covariates**

Age at diagnosis was categorized as ≤40, 41-50, 51-60, 61-70, 70+ (Murphy et al., 2016) to fully account for differences by age. Insurance status was categorized as Uninsured, Medicaid, Medicare, Other Government and Private. Instead of arbitrarily categorizing period of diagnosis, we dichotomized it into two categories based on the landmark Affordable Care Act (Pre-ACA 2004-2010, and Post-ACA 2011-2013) as these two time periods may be different in terms of patients' access to care, possibly determining whether HPV testing was done or not. This categorization was used for most of the analysis, except for a sub-analysis of HPV unknown status in OPCs, where year of diagnosis was included as a continuous variable because it had a linear relationship with HPV unknown status.

Two zip code level variables, education (percentage of adults without high school diploma in patient's zip code) and income (median household income in patient's zip code), based on the 2012 American Community Survey (2008-2012) were studied by quartiles. These area level SES variables, along with insurance, served as a proxy for individual level SES in our analysis. Since region of residence can affect a person's exposure to certain risk factors, it was included in the study. Rural region of residence was based on patients' area FIPS code (documented at the time of diagnosis) matched against US Department of Agriculture's (USDA) classification scheme (Peterson et al., 2016; USDA Economic Research Service, 2004). No information was available on geographic area of the patient; however, geographic area of the reporting facility is included in NCDB. To account for the geographic differences in distribution of racial/ethnic groups, site of cancer, and HPV as a risk factor, geographic area of the reporting facility was included in the analysis. It was categorized into four areas: Midwest, Northeast, South and West.

3. Statistical Analyses

a. Distribution of Characteristics by Race/Ethnicity

After univariate analyses were performed to examine the distribution of variables and the proportion of missing observations, bivariate analyses were done to examine the distribution of various demographic and clinical characteristics by race/ethnicity. Chi square test was used to assess racial/ethnic differences in the distribution of categorical variables and one-way ANOVA was used to assess racial/ethnic differences in mean age at diagnosis.

b. Association of Race/Ethnicity with Site Group

Bivariate association of site group was examined with all the independent predictors, including race/ethnicity (See Figure 1 for conceptual model). Assessment of effect modification was limited by the extremely small sample sizes in two of the groups (American Indian and Pacific Islanders) upon stratification by *a priori* selected potential effect modifiers (area level income, area level education and age at diagnosis). Race/ethnicity (as the main exposure) along with all the potential confounders were included in the initial multinomial logistic model for site group. Manual backward selection was then used to obtain a final model to get Odds Ratios (OR) with 95% confidence intervals (CI). Covariates were dropped from the model one at a time to assess whether any of the exposure level ORs changed by 10%. If the ORs changed by $\geq$10%, the variable was retained as a confounder. Area level income, insurance and geographic area were confounders in the model, so they were retained. Although age and area level education were not confounders based on the model, they are strong conceptual confounders and adding them to the model improved the Akaike Information Criterion (AIC),

which is a method of comparing models to select a better fitting model. Therefore, age and area level education were also included in the final model.

c. **Association of Race/Ethnicity with HPV Status in OPC Cases**

Among OPC cases, bivariate association of HPV status was examined with all the independent predictors, including race/ethnicity. Stratified analysis was explored preliminarily; however, upon stratification some of the racial/ethnic groups had extremely small sample sizes. Therefore, stratification was not done for the main analysis of race/ethnicity with HPV status. Moreover, due to small sample size, Pacific Islander group was not included in the further analysis of HPV status. For the main analysis, a multivariate multinomial logistic model that included race/ethnicity and the other potential predictors of HPV 16/18 status was created. Manual backward selection was used in the manner described in section 3b (i.e., Statistical Analyses: Association of Race/Ethnicity with Site Group). Area level income, insurance and age were confounders in the model. Although period of diagnosis was not a confounder in the model, it was included in the final model because it is a strong conceptual confounder, that allows us to control for unknown covariates in diagnosis and access to care, and improved AIC tremendously. The model selected above was re-run with five category HPV outcome variable to compare the two results. A sub-analysis was done to compare unknown HPV status with known HPV status among OPC cases diagnosed from 2010 – 2013 (because routine reporting of HPV to NCDB started in 2010, even though cases were reported prior to 2010).

d. **Examining Temporal Trends**

Trends in HNSCCs were assessed by calculating Annual Percentage Change (APC). The trends for HNSCCs by site group (2004 – 2013), and by HPV status (among OPC

cases from 2009 – 2013) were studied for all the racial/ethnic groups. The APCs were "calculated by fitting a least squares regression line to the natural logarithm" of annual rates (NCI SEER, n.d.). The annual rates were calculated by dividing the number of cases of HNSCC of a particular site group by the total number of annual HNSCC cases (and cases of a particular HPV status by the total number of annual OPC cases) for that subpopulation (Peterson et al., 2016). Data were analyzed using SAS 9.4 (SAS Institute, Cary NC). Microsoft excel was used for creating graphs for trends.

C. **Results**

From 2004 to 2013, there were 156,927 (81.6%) NHW, 21,379 (11.1%) NHB, 8,861 (4.6%) Hispanic (White and Black), 603 (0.3%) American Indian, 4,308 (2.2%) Asian and 249 (0.1%) Pacific Islander males diagnosed with HNSCC. Demographic and clinical characteristics of the study population by race/ethnicity are presented in Table III; p value for the association of all variables with race/ethnicity was <0.001. Pacific Islander and Asian males had lower mean age at diagnosis, however, the most striking difference was in diagnosis by age 40. Asian and Pacific Islander males had two to four-fold higher likelihood of diagnosis by age 40 when compared to other racial/ethnic groups ($p<0.001$).

Asian, Pacific Islander and NHW males were better off in terms of insurance, area level income and area level education. While Asians were more likely to have Non-OPC and OCC, NHB had higher likelihood of laryngeal cancer and NHW had higher likelihood of OPC. Moreover, HPV 16/18 positive OPCs were most common in NHW, while HPV 16/18 negative OPCs were more common in Asians.

TABLE III

DISTRIBUTION OF DEMOGRAPHIC VARIABLES, SITE AND HPV STATUS AMONG MALE HNSCC CASES FROM VARIOUS RACIAL/ETHNIC GROUPS USING NATIONAL CANCER DATABASE, 2004 - 2013

	NHW Males (n=156927)	NHB Males (n=21379)	Hispanic[a] Males (n=8861)	American Indian Males (n=603)	Asian Males (n=4308)	Pacific Islander Males (n=249)
Age at diagnosis						
Mean [SD]	61 [11]	59 [11]	60 [12]	59 [11]	58 [14]	56 [12]
Age group						
≤40	4009 (2.6)	692 (3.2)	489 (5.5)	19 (3.2)	508 (11.8)	27 (10.8)
41-50	22852 (14.6)	3502 (16.4)	1405 (15.9)	105 (17.4)	785 (18.2)	58 (23.3)
51-60	53306 (34.0)	7861 (36.8)	2781 (31.4)	227 (37.6)	1213 (28.2)	72 (28.9)
61-70	44806 (28.6)	6164 (28.8)	2406 (27.2)	165 (27.4)	961 (22.3)	60 (24.1)
>70	31954 (20.4)	3160 (14.8)	1780 (20.1)	87 (14.4)	841 (19.5)	32 (12.8)
Insurance[b]						
Private	71180 (46.9)	5862 (28.6)	2810 (33.7)	166 (28.5)	2129 (51.1)	114 (47.1)
Other Govt	3782 (2.5)	529 (2.6)	98 (1.2)	103 (17.7)	28 (0.7)	7 (2.9)
Medicare	55382 (36.5)	7116 (34.7)	2672 (32.0)	184 (31.6)	1017 (24.4)	57 (23.6)
Medicaid	12576 (8.3)	4633 (22.6)	1645 (19.7)	88 (15.1)	650 (15.6)	50 (20.7)
Uninsured	8959 (5.9)	2356 (11.5)	1115 (13.4)	41 (7.0)	344 (8.2)	14 (5.8)
Missing	5048	883	521	21	140	7
Period of Diagnosis						
Pre ACA (2004-10)	103468 (65.9)	14661 (68.6)	5873 (66.3)	378 (62.7)	2794 (64.9)	162 (65.1)
Post ACA (2011-13)	53459 (34.1)	6718 (31.4)	2988 (33.7)	225 (37.3)	1514 (35.1)	87 (34.9)
Area level Median Household Income[c]						
$63,000+	46195 (29.9)	2336 (11.1)	1573 (18.0)	88 (14.7)	2000 (47.2)	124 (50.6)
$48,000-$62,999	42688 (27.6)	3248 (15.4)	2163 (24.8)	128 (21.4)	1113 (26.3)	75 (30.6)
$38,000-$47,999	39764 (25.8)	4710 (22.4)	2260 (25.9)	141 (23.6)	677 (16.0)	27 (11.0)
<$38,000	25731 (16.7)	10749 (51.1)	2732 (31.3)	240 (40.2)	443 (10.5)	19 (7.8)
Missing	2549	336	133	6	75	4
Area level education (% with No HSD)[d]						
<7%	35794 (23.2)	1255 (6.0)	704 (8.1)	73 (12.2)	960 (22.7)	64 (26.1)
7-12.9%	52573 (34.0)	3410 (16.2)	1388 (15.9)	167 (28.0)	1198 (28.3)	86 (35.1)
13-20%	42266 (27.4)	7714 (36.6)	1999 (22.9)	189 (31.7)	916 (21.6)	60 (24.5)
>=21%	23839 (15.4)	8681 (41.2)	4644 (53.2)	168 (28.1)	1160 (27.4)	35 (14.3)
Missing	2455	319	126	6	74	4
Rural Residence[e]						
Yes	10371 (6.8)	711 (3.4)	190 (2.2)	117 (19.9)	58 (1.4)	19 (8.0)
No	141163 (93.2)	20155 (96.6)	8442 (97.8)	472 (80.1)	4099 (98.6)	220 (92.0)
Missing	5393	513	229	14	151	10
Geographic area of Reporting Facility[f]						
Midwest	40489 (26.4)	4304 (20.7)	663 (7.8)	162 (27.7)	455 (11.8)	24 (10.5)
North East	29278 (19.1)	2975 (14.3)	1747 (20.7)	36 (6.2)	918 (23.8)	17 (7.4)
South	60945 (39.7)	12405 (59.6)	3597 (42.6)	191 (32.6)	698 (18.1)	36 (15.7)
West	22887 (14.9)	1115 (5.4)	2441 (28.9)	196 (33.5)	1783 (46.3)	152 (66.4)
Missing	3328	580	413	18	454	20

TABLE III (Continued)

DISTRIBUTION OF DEMOGRAPHIC VARIABLES, SITE AND HPV STATUS AMONG MALE HNSCC CASES FROM VARIOUS RACIAL/ETHNIC GROUPS USING NATIONAL CANCER DATABASE, 2004 - 2013

	NHW Males (n=156927)	NHB Males (n=21379)	Hispanic[a] Males (n=8861)	American Indian Males (n=603)	Asian Males (n=4308)	Pacific Islander Males (n=249)
Primary Site of Tumor						
Lip	5147 (3.3)	75 (0.4)	230 (2.6)	8 (1.3)	24 (0.6)	2 (0.8)
Gum/FOM/OtherM	18702 (11.9)	2631 (12.3)	1151 (13.0)	73 (12.1)	638 (14.8)	25 (10.0)
Tongue (Anterior)	14736 (9.4)	1080 (5.1)	806 (9.1)	44 (7.3)	518 (12.0)	26 (10.4)
Tongue (Base)	24295 (15.5)	2056 (9.6)	906 (10.2)	66 (11.0)	228 (5.3)	26 (10.4)
Tonsil	28313 (18.0)	2688 (12.6)	1362 (15.4)	108 (17.9)	335 (7.8)	27 (10.8)
Oropharynx	5894 (3.8)	1175 (5.5)	334 (3.8)	21 (3.5)	76 (1.8)	3 (1.2)
Nasopharynx	4194 (2.7)	1034 (4.8)	430 (4.8)	35 (5.8)	1484 (34.4)	79 (31.7)
Hypopharynx	7511 (4.8)	1829 (8.6)	508 (5.8)	49 (8.1)	199 (4.6)	13 (5.2)
Other Pharynx	1926 (1.2)	301 (1.4)	105 (1.2)	11 (1.8)	29 (0.7)	5 (2.0)
Larynx	46209 (29.4)	8510 (39.8)	3029 (34.2)	188 (31.2)	777 (18.0)	43 (17.3)
Site group[g]						
Oral Cavity	38585 (24.6)	3786 (17.7)	2187 (24.7)	125 (20.7)	1180 (27.4)	53 (21.3)
Oropharynx	58502 (37.3)	5919 (27.7)	2602 (29.4)	195 (32.3)	639 (14.8)	56 (22.5)
Non-Oropharynx	13631 (8.7)	3164 (14.8)	1043 (11.8)	95 (15.8)	1712 (39.7)	97 (39.0)
Larynx	46209 (29.4)	8510 (39.8)	3029 (34.2)	188 (31.2)	777 (18.0)	43 (17.3)
HPV[h] status (OPC cases, 2009 - 2013)						
HPV 16/18 positive	6889 (20.1)	329 (10.1)	199 (13.4)	17 (13.1)	54 (14.1)	8 (20.5)
HPV 16/18 negative	7787 (22.7)	713 (22.0)	320 (21.5)	19 (14.6)	89 (23.2)	4 (10.3)
HPV unknown	19591 (57.2)	2206 (67.9)	970 (65.1)	94 (72.3)	240 (62.7)	27 (69.2)

[a] Includes Hispanic Whites and Blacks only.

[b] Represents primary payer at diagnosis.

[c] Based on 2012 American Community Survey (2008-2012, adjusted for 2012 inflation) median household income in the patient's zip code area.

[d] Based on 2012 American Community Survey (2008-2012) percentage of adults without high school diploma in patient's zip code area.

[e] Rurality and urban influence is based on adjacency to metro area determined by matching the patients' area FIPS code (recorded at the time of diagnosis) against 2003 USDA Economic Research Service. Rural areas include those that were completely rural counties non-adjacent to a metro area or urban population (of any size) non-adjacent to a metro area. Urban includes counties in metro areas (of any population size) or urban population (of any size)/completely rural population adjacent to a metro area (USDA Economic Research Service, 2004).

[f] Midwest represents Ohio, Michigan, Indiana, Wisconsin, Illinois, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska and Kansas. North East represents Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey and Pennsylvania. South includes Delaware, District of Columbia, Maryland, Virginia, West Virginia, Kentucky, North Carolina, South Carolina, Tennessee, Georgia, Florida, Alabama, Mississippi, Arkansas, Louisiana, Texas and Oklahoma. West includes Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, California, Oregon, Washington, Alaska and Hawaii (US Census Bureau, n.d.) .

[g] Oral Cavity includes lips, anterior tongue, gums, buccal mucosa, hard palate, and other mouth; Oropharynx includes base of tongue, tonsils besides oropharynx; Non-oropharynx includes nasopharynx, hypopharynx and other pharynx

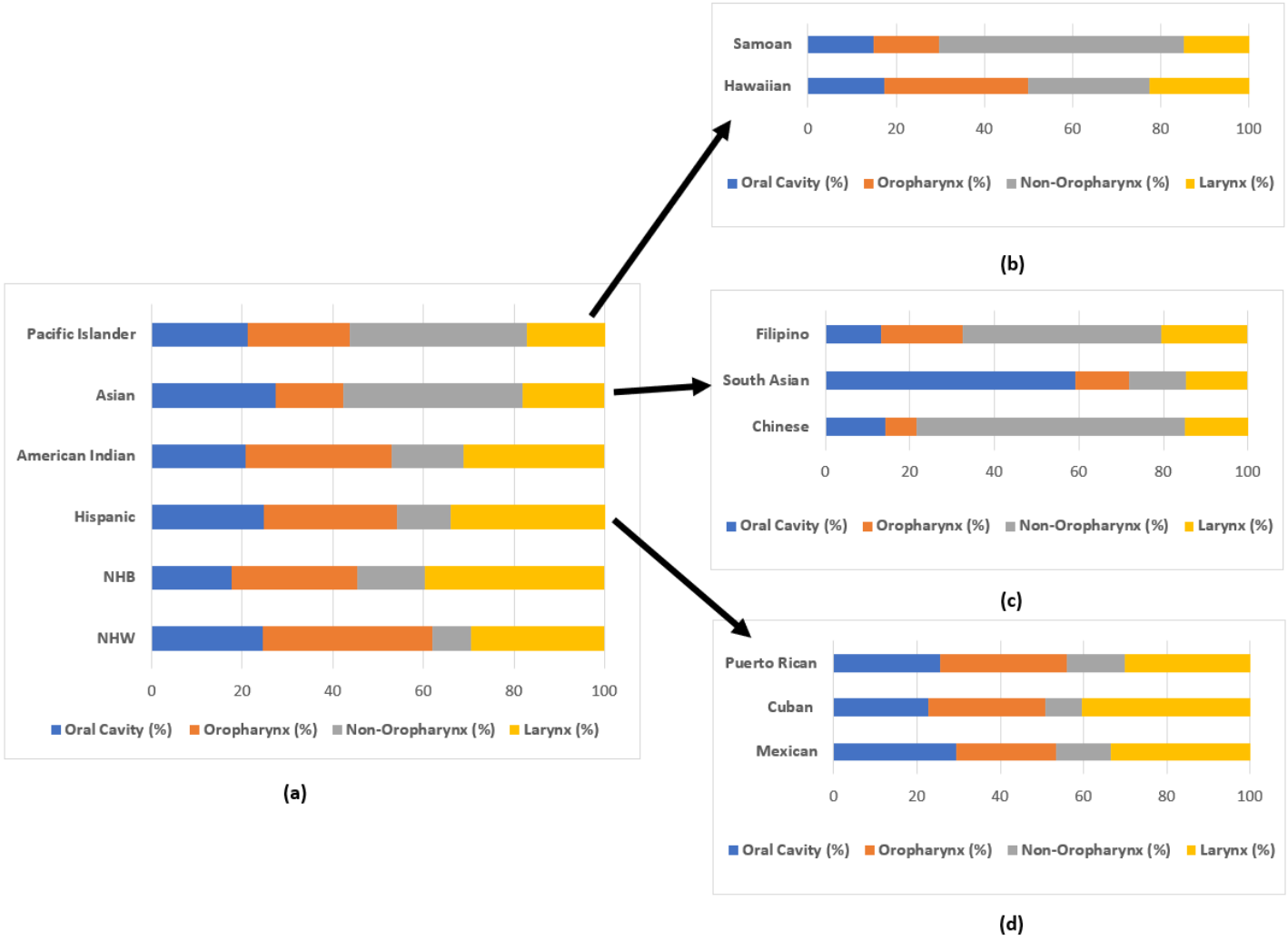
[h] HPV 16/18 positive represents cases that were positive for HPV 16 or HPV 18 or both, HPV 16/18 negative represents cases that were negative for both HPV 16 and 18 but could be positive for HPV types other than 16/18 (includes "HPV negative for high-risk and low-risk types, HPV negative for high-risk types with no mention of low-risk types, Negative NOS", "HPV positive for low-risk types only", "HPV positive for specified high risk type(s) other than types 16 or 18", "HPV positive for high-risk type(s), NOS, high-risk type(s) not stated", HPV positive NOS risk and type(s) not stated") and HPV unknown includes "Not applicable: Information not collected for this case", "Test ordered, results not in chart", "Test not done (test was not ordered and was not performed), including no pathologic specimen available for HPV testing", "Unknown or no information" ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

Figure 3 shows the distribution of site group by race/ethnicity. The largest group among Hispanic (White and Black) cases consisted of non-specified Spanish, Hispanic and Latino (59%). Among the three largest Hispanic groups with specified ethnic origin (namely Mexican (14%), Cuban (9%) and Puerto Rican (6%)), OPC was least common in Mexicans and was strikingly lower than NHW (24% vs. 37%). On the contrary, laryngeal cancer was more likely in Cubans (40% vs. 29% in NHW).

When we examined subsites, lip cancer was less likely in Puerto Ricans (0.9%) compared to other large Hispanic groups (4% in Mexicans and 3% in Cuban) and NHW (3%). Another interesting finding was that Mexicans had a much higher likelihood of diagnosis by age $\leq$50 (23%; of these 5.7% were by age $\leq$40) compared to the other two Hispanic groups (14% (of which 1.7% were by age $\leq$40) in Puerto Ricans and 13% (of which 2.2% were by age $\leq$40) in Cubans) and NHW (17%; of which 2.6% were by age $\leq$40) (Table XV in Appendix A). Overall, Mexicans were more likely to be of HPV unknown status, compared to Cubans, Puerto Ricans as well as NHW. This pattern persisted even when the data were limited to OPC cases diagnosed 2010 onwards only (70% in Mexican vs. 42% in Cuban and 56% in Puerto Rican). Cubans had a relatively higher likelihood of HPV 16/18 positive OPCs (2010 - 2014) than the other two groups (15% vs. 10% in both Puerto Rican and Mexican).

Of 4,308 Asians, 24.3% were Chinese, 20.6% were South Asian Indian/Pakistani (I/P) and 11.6% were Filipino, comprising the three largest Asian subgroups (barring the Other Asian and non-specified Asians subgroup, 17.3%). Vietnamese (10%), Japanese (7%) and Korean (5%) were other large Asian subgroups. Figure 3c presents the distribution of HNSCC site group in the three largest Asian subgroups in the US. South Asian I/P had a much higher proportion of OCC

Figure 3: Distribution of HNSCC site group among – (a) racial/ethnic groups, (b) two largest Pacific Islander subgroups, (c) three largest Asian subgroups, and (d) three largest Hispanic subgroups in the US.



(59%), compared to all the other Asian groups (two times higher than Japanese and Koreans, four times higher than Chinese and Filipinos, and five times higher than Vietnamese) and (two times higher than) NHW. Certain Asian subgroups, including Chinese, Vietnamese, Filipino (and of the smaller Asian groups, Hmong, Thai and Laotian) had a much higher likelihood of Non-OPC compared to NHW. Chinese (63.5%) had seven times higher proportion of Non-OPCs compared to NHW (8.7%). Hmong (n=32) had fewer number of total HNSCC cases but 87.5% of these were Non-OPC, which was the highest among all Asian subgroups.

Of 249 Pacific Islander males, 24.5% were non-specified, while 44% were Hawaiian and 10.8% were Samoan. Compared to NHW males, both Hawaiians (33% vs. 9%) and Samoans (56% vs. 9%) were more likely to have Non-OPC. While these Non-OPC cases among Samoans were exclusively due to nasopharynx, for Hawaiians both nasopharynx (14% vs. 3% in NHW) and hypopharynx (11% vs. 5% in NHW) were more likely to be a subsite for HNSCC, when compared to NHW. When OPC cases diagnosed 2010 onwards were examined, 55% of Hawaiians were of unknown HPV status, while 28% were HPV 16/18 positive and 17% were HPV 16/18 negative.

1. **Race/Ethnicity and Site Group**

Using OPC as a referent site group, after adjusting for covariates (age at diagnosis, area level income quartiles, area level education quartiles, insurance and geographic area of reporting facility), Asian males had 11 times higher odds (OR_{adj}=11.1; 95% CI: 10.0 – 12.3) of being diagnosed with Non-OPC when compared to NHW. As we were expecting, odds for OCC were also higher among Asians. Similarly, Pacific Islanders had eight times higher odds (OR_{adj}=7.9; 95% CI: 5.6 – 11.2) of having Non-OPC (vs. OPC). When compared to NHW, NHB males had lower odds of being diagnosed with OCC but surprisingly, had higher odds of being diagnosed

with not only laryngeal (OR_{adj}=1.6; 95% CI:1.5 – 1.6) tumor, but also Non-OPC (OR_{adj}=1.9; 95% CI 1.8 – 2.0). Table IV presents the results of multinomial model.

TABLE IV
ASSOCIATION OF RACE/ETHNICITY WITH SITE GROUP AFTER CONTROLLING FOR CONFOUNDERS IN A MULTINOMIAL MODEL

	Adjusted OR (95% CI)[a]		
	Oral Cavity[b] vs. Oropharynx[c]	**Non-Oropharynx[d] vs. Oropharynx[c]**	**Larynx vs. Oropharynx[c]**
NHW	**1.00 (reference)**	**1.00 (reference)**	**1.00 (reference)**
NHB	**0.92 (0.88 – 0.96)**	**1.89 (1.79 – 1.99)**	**1.58 (1.52 – 1.64)**
Hispanic[e]	**1.15 (1.08 – 1.23)**	**1.43 (1.31 – 1.55)**	**1.34 (1.26 – 1.42)**
Asian	**3.00 (2.70 – 3.33)**	**11.09 (10.01 – 12.29)**	**1.91 (1.71 – 2.14)**
American Indian	1.03 (0.81 – 1.31)	**1.96 (1.51 – 2.55)**	**1.32 (1.07 – 1.64)**
Pacific Islander	**1.52 (1.01 – 2.28)**	**7.91 (5.56 – 11.23)**	1.43 (0.94 – 2.17)

[a] Adjusted for age, area level income quartiles, area level education quartiles, insurance and geographic area of reporting facility.
[b] Oral Cavity includes lips, anterior tongue, gums, buccal mucosa, hard palate, and other mouth.
[c] Oropharynx includes base of tongue, tonsils besides oropharynx.
[d] Non-oropharynx includes nasopharynx, hypopharynx and other pharynx.
[e] Includes Hispanic Whites and Blacks only.

2. Race/Ethnicity and HPV Status among OPC Cases

For the association of race/ethnicity with HPV status, Asians (OR_{crude}=0.7; 95% CI: 0.5 – 1.0), Hispanics (OR_{crude}=0.7; 95% CI: 0.6 – 0.8) and NHB (OR_{crude}=0.5; 95% CI: 0.5 – 0.6), had significantly lower odds of having HPV 16/18 positive OPC compared to NHW in the crude

analysis. Similar pattern was observed in multinomial adjusted analysis (with HPV 16/18 negative as the referent status) where NHB, Hispanics and Asians had significantly lower odds of being HPV 16/18 positive, with NHB having the lowest odds (OR_{adj}=0.6; 95% CI: 0.5 – 0.7), in comparison to NHW. These minority racial/ethnic groups had lower odds of other HPV types as well. Figure 4 presents the association of HPV 16/18 status with race/ethnicity for OPC, adjusted for age at diagnosis, period of diagnosis, insurance status and area level income quartiles (Figure representing HPV status for other sites is included in Appendix C). Table V presents the crude and adjusted results.

Figure 4: Association of race/ethnicity with HPV status among OPC cases.

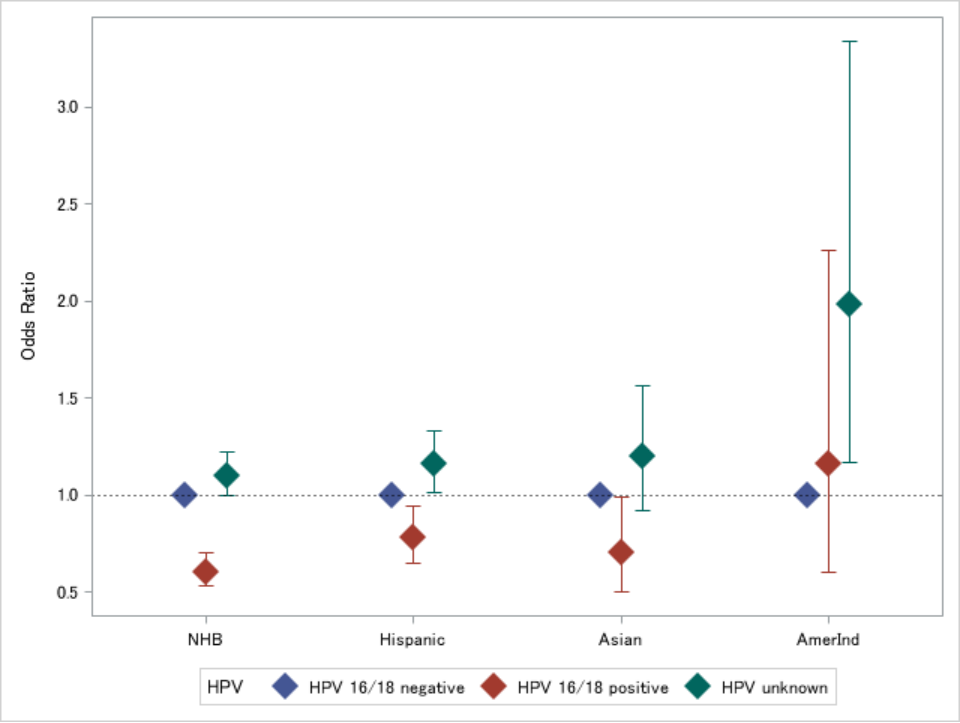


TABLE V

CRUDE AND ADJUSTED ASSOCIATION OF RACE/ETHNICITY WITH HPV STATUS AMONG OROPHARYNGEAL CANCER CASES USING NATIONAL CANCER DATABASE, 2009 - 2013.

	NHB vs. NHW OR (95% CI)	Hispanic[a] vs. NHW OR (95% CI)	American Indian vs. NHW OR (95% CI)	Asian vs. NHW OR (95% CI)
CRUDE				
HPV 16/18 negative[c]	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
HPV 16/18 positive[b]	**0.52 (0.46 – 0.60)**	**0.70 (0.59 – 0.84)**	1.01 (0.52 – 1.95)	**0.69 (0.49 – 0.96)**
HPV unknown[d]	**1.23 (1.13 – 1.34)**	**1.20 (1.06 – 1.37)**	**1.97 (1.20 – 3.22)**	1.07 (0.84 – 1.37)
ADJUSTED[h]				
HPV 16/18 negative[c]	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
HPV 16/18 positive[b]	**0.60 (0.53 – 0.70)**	**0.78 (0.65 – 0.94)**	1.16 (0.60 – 2.26)	**0.70 (0.50 – 0.99)**
HPV unknown[d]	1.10 (1.00 – 1.22)	**1.16 (1.00 – 1.33)**	1.98 (1.17 – 3.34)	1.20 (0.92 - 1.56)
ADJUSTED[i]				
HPV (all) negative[g]	1.00 (ref)	1.00 (ref)	--[j]	1.00 (ref)
HPV 16/18 positive[b]	**0.44 (0.38 – 0.52)**	**0.64 (0.52 – 0.79)**		**0.53 (0.36 – 0.78)**
HPV other HR positive[e]	**0.34 (0.25 – 0.45)**	**0.56 (0.39 – 0.79)**		0.71 (0.40 – 1.24)
HPV LR positive[f]	**0.48 (0.39 – 0.59)**	**0.67 (0.51 – 0.88)**		**0.40 (0.22 – 0.73)**
HPV unknown[d]	**0.81 (0.73 – 0.91)**	0.95 (0.81 – 1.12)		0.92 (0.67 - 1.24)

[a] Includes Hispanic Whites and Blacks only.

[b] HPV 16/18 positive represents cases that were positive for HPV 16 or HPV 18 or both.

[c] HPV 16/18 negative represents cases that were negative for both HPV 16 and 18 but could be positive for HPV types other than 16/18 (includes "HPV negative for high-risk and low-risk types, HPV negative for high-risk types with no mention of low-risk types, Negative NOS", "HPV positive for low-risk types only", "HPV positive for specified high risk type(s) other than types 16 or 18", "HPV positive for high-risk type(s), NOS, high-risk type(s) not stated", HPV positive NOS risk and type(s) not stated") ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

[d] HPV unknown includes "Not applicable: Information not collected for this case", "Test ordered, results not in chart", "Test not done (test was not ordered and was not performed), including no pathologic specimen available for HPV testing", "Unknown or no information" ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

[e] HPV other High Risk+ includes HPV positive for High Risk types other than 16/18 or positive for high risk type NOS.

[f] HPV low risk+ includes HPV positive for low risk types only or HPV positive NOS.

[g] HPV (all) negative includes "negative for high-risk and low-risk types" or "negative for high-risk types with no mention of low-risk type" or "HPV Negative, NOS" ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

[h] Adjusted for age at diagnosis, period of diagnosis, insurance status and area level income quartiles.

[i] Reran model (a) with five category HPV status as outcome.

[j] Sample was lower than 10 for some categories so these racial/ethnic groups were not included in this analysis.

We conducted further analyses to ascertain factors associated with non-receipt of HPV testing (Table VI). These analyses were limited to OPC cases from 2010 – 2013 because routine reporting started in 2010. In these analyses, all the minority racial/ethnic groups were more likely to have unknown HPV status, but the likelihood was highest in American Indians, in comparison to NHW. It was also interesting to note that there was a linear association of area-level education, area-level income and year of diagnosis with Unknown status. Those with higher area level education and higher area level median income and a more recent year of diagnosis, were less likely to have unknown HPV status.

3. **Temporal Trends**

While the total number of HNSCC cases for NHW males (Figure 5a) increased from 13,281 to 18,410 during 2004 to 2013, a significant increase was observed in OPC cases only from 4,183 in 2004 to 7,639 in 2013 (APC=3.17; $p<0.001$). During the same interval, the proportion of OCC (APC=-0.59; p=0.012), non-OPC (APC=-1.76; p=0.006), and laryngeal (APC=-2.77; $p<0.001$) decreased significantly. Primary Y-axis represents total HNSCC cases and secondary Y-axis represents number of HNSCC cases for each site group.

For NHB males (Figure 5b), the total number of cases increased from 2052 to 2266 during 2004-2013. While the number of diagnoses of OCC, non-OPC and laryngeal cancer remained relatively unchanged, the proportion of OPC increased significantly in NHB males (554 cases in 2004 to 667 cases in 2014; APC=1.76; p=0.006). For Hispanic males (Figure 5c), the proportion of OPC (APC=1.97; p=0.001) increased while the proportion of laryngeal cancer (APC=-1.49; p=0.028) decreased from 2004 to 2013.

TABLE VI

COMPARISON OF OROPHARYNGEAL CASES WITH UNKNOWN HPV STATUS TO THOSE WITH KNOWN HPV STATUS, 2010 – 2013[a]

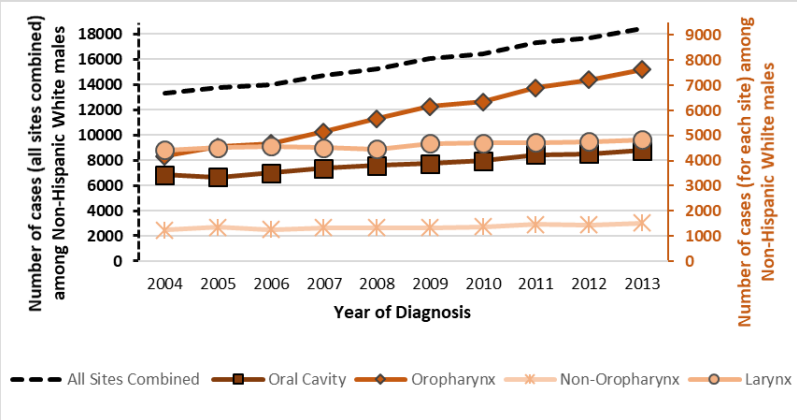
	Crude OR (95% CI)	**Adjusted OR[b] (95% CI)**
Race/ethnicity		
NHW	1.00 (reference)	1.00 (reference)
NHB	**1.63 (1.51 – 1.77)**	**1.29 (1.18 – 1.41)**
Hispanic[c]	**1.47 (1.31 – 1.65)**	**1.20 (1.05 – 1.36)**
American Indian	**2.19 (1.47 – 3.26)**	**1.99 (1.29 – 3.08)**
Asian	**1.33 (1.06 – 1.67)**	**1.36 (1.07 – 1.74)**
Pacific Islander	1.62 (0.78 – 3.36)	1.47 (0.67 – 3.26)
Age at diagnosis		
≤40	1.00 (reference)	1.00 (reference)
41 – 50	1.08 (0.90 – 1.29)	1.18 (0.97 – 1.44)
51 – 60	1.18 (1.00 – 1.41)	**1.35 (1.12 – 1.64)**
61 – 70	**1.34(1.13 – 1.59)**	**1.54 (1.27 – 1.86)**
>70	**1.84 (1.54 – 2.20)**	**2.05 (1.67 – 2.52)**
Insurance		
Private Insurance	1.00 (reference)	1.00 (reference)
Medicare	**1.65 (1.57 – 1.74)**	**1.37 (1.28 – 1.47)**
Medicaid	**2.02 (1.87 – 2.18)**	**1.78 (1.64 – 1.94)**
Other Government	**2.15 (1.88 – 2.46)**	**2.01 (1.74 – 2.31)**
Not Insured	**1.93 (1.76 – 2.12)**	**1.84 (1.67 – 2.03)**
Area level Median Household Income		
$63,000+	1.00 (reference)	---
$48,000-$62,999	1.27 (1.20 – 1.35)	
$38,000-$47,999	1.56 (1.47 – 1.66)	
<$38,000	1.80 (1.69 – 1.92)	
Area level education (% with No HSD)		
<7%	1.00 (reference)	1.00 (reference)
7-12.9%	**1.26 (1.18 – 1.33)**	**1.26 (1.18 – 1.34)**
13-20%	**1.62 (1.53 – 1.73)**	**1.55 (1.45 – 1.66)**
>=21%	**2.01 (1.87 – 2.16)**	**1.74 (1.61 – 1.89)**
Geographic Area of Reporting Facility		
Midwest	1.00 (reference)	---
North East	0.71 (0.66 – 0.76)	
South	**1.20 (1.14 – 1.27)**	
West	0.94 (0.88 – 1.01)	
Residence		
Urban	1.00 (reference)	---
Rural	**1.29 (1.17 – 1.42)**	
Year of Diagnosis		
2013	1.00 (reference)	1.00 (reference)
2012	**1.27 (1.19 – 1.35)**	**1.28 (1.20 – 1.37)**
2011	**1.96 (1.85 – 2.09)**	**2.05 (1.92 – 2.19)**
2010	**3.66 (3.43 – 3.90)**	**4.03 (3.76 – 4.32)**

[a] This analysis was limited to OPC cases diagnosed from 2010 to 2013 only because currently testing for HPV is recommended for OPC cases only and required reporting of HPV status to NCDB started in 2010.

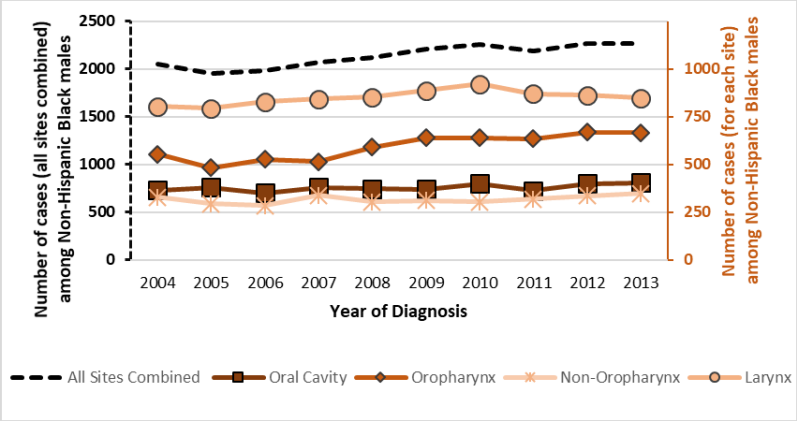
[b] Mutually adjusted

[c] Includes Hispanic Whites and Blacks only.

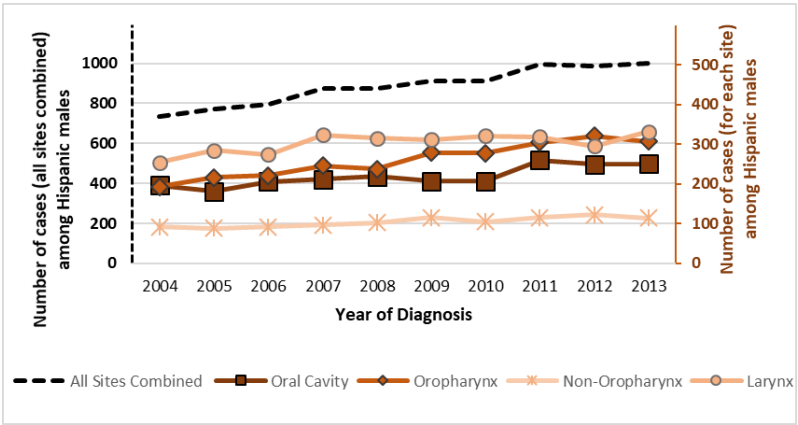
Figure 5: Temporal trends in HNSCC cases among males of various racial/ethnic groups by site group in the US



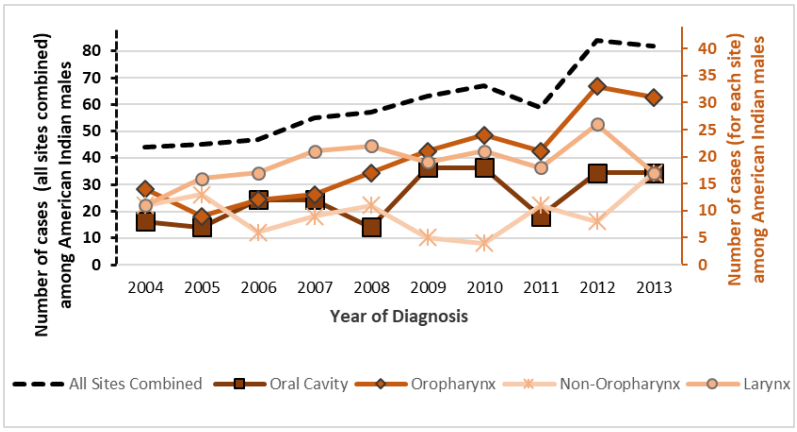
5a) HNSCCs by site group among NHW males



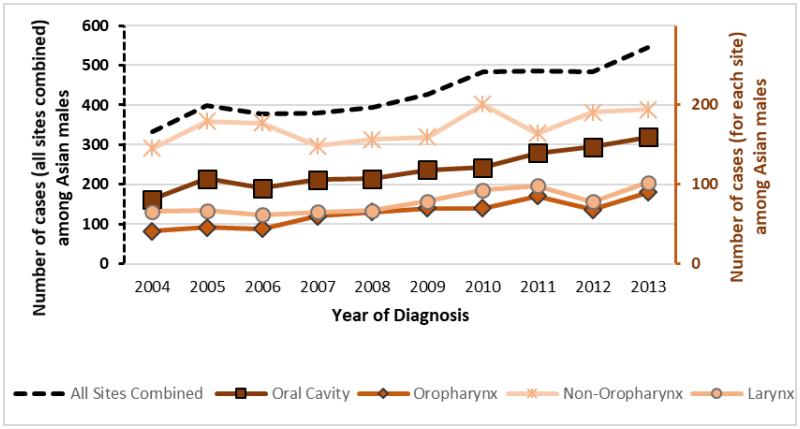
5b) HNSCCs by site group among NHB males



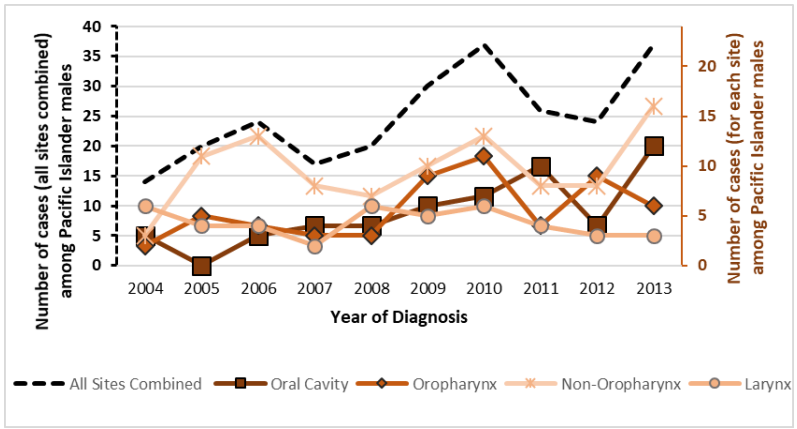
5c) HNSCCs by site group among Hispanic (White and Black) males



5d) HNSCCs by site group among American Indian males



5e) HNSCCs by site group among Asian males

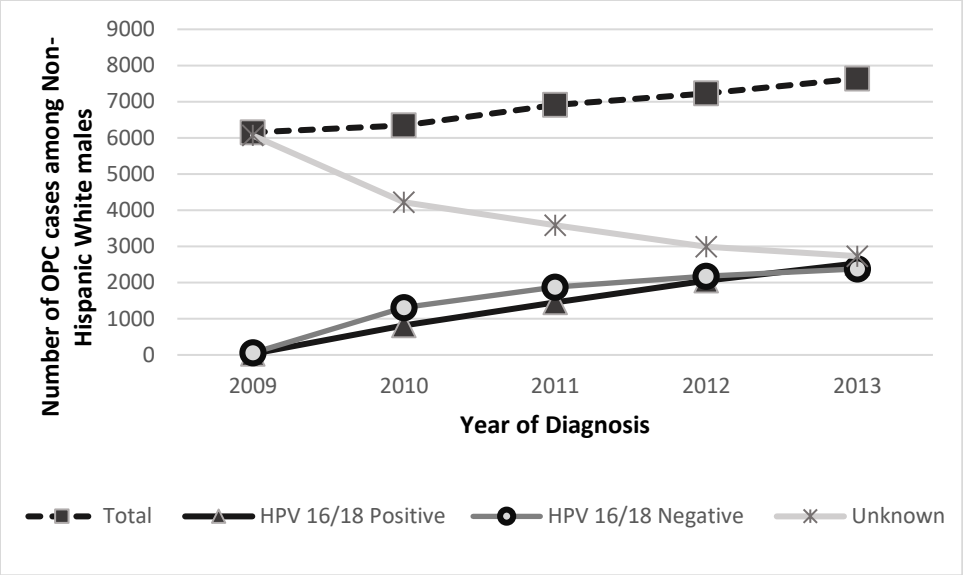


5f) HNSCCs by site group among Pacific Islander males

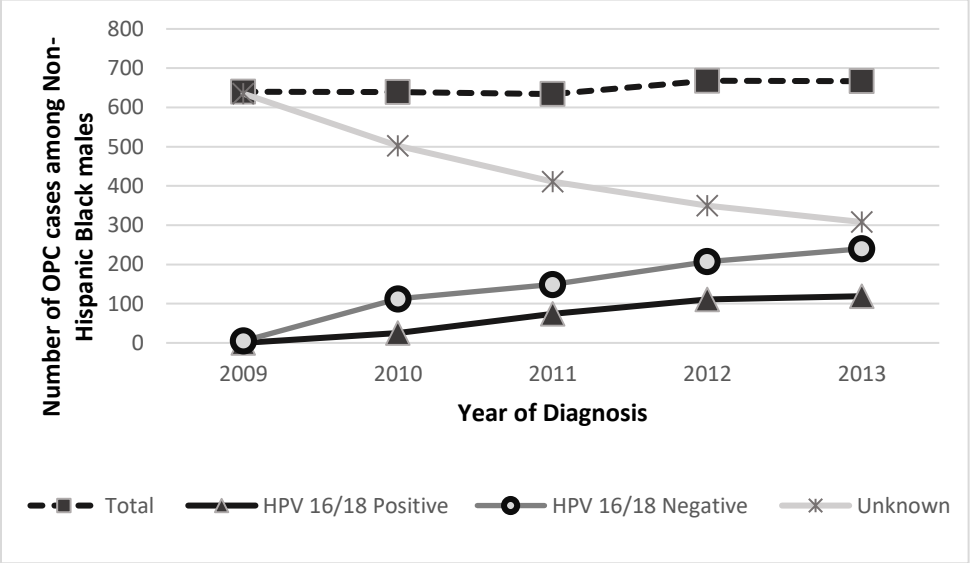
For Asian males (Figure 5e), the total number of cases increased from 333 to 545 from 2004 to 2013. The proportion of OCC (APC=1.74; p=0.018) and OPC (APC=3.58; p=0.03) increased, while the proportion of non-OPC decreased (APC=-2.55; p=0.01). For American Indians, the number of cases (all sites) increased from 44 in 2004 to 82 in 2013 and the proportion of OPC cases increased significantly with an APC of 5.80 (p=0.0095).

Figure 6 shows the trends in OPCs by HPV status from 2009 to 2013. For all the racial/ethnic groups except Pacific Islanders, the number of HPV 16/18 positive cases have increased consistently along with a concomitant decrease in tumors with unknown HPV status. For most racial/ethnic groups, the number of HPV 16/18 negative tumors also increased from 2009 to 2013. For NHW (Figure 6a) and NHB (Figure 6b), the proportional increase in HPV 16/18 negative and positive tumors was not significant ($p>0.05$ for both). For Asian males, although the increase in HPV 16/18 positive OPCs was significant (p=0.03), the numbers were too low, from one (HPV 16/18 positive OPC) case in 2009 to 24 cases in 2013. Similarly, for Hispanic males, the increase in HPV positive OPCs was significant (p=0.04); however, these increasing trends were accompanied by decreasing trend in HPV unknown cases. For Pacific Islanders, no clear pattern was noticed by HPV status.

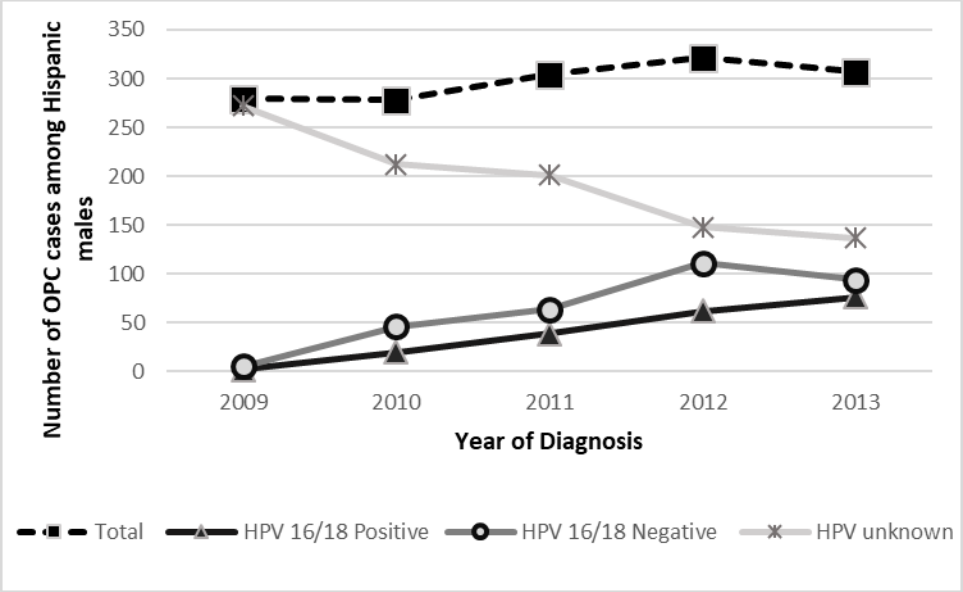
Figure 6: Temporal trends by HPV status among oropharyngeal cancer cases in males of various racial/ethnic groups.



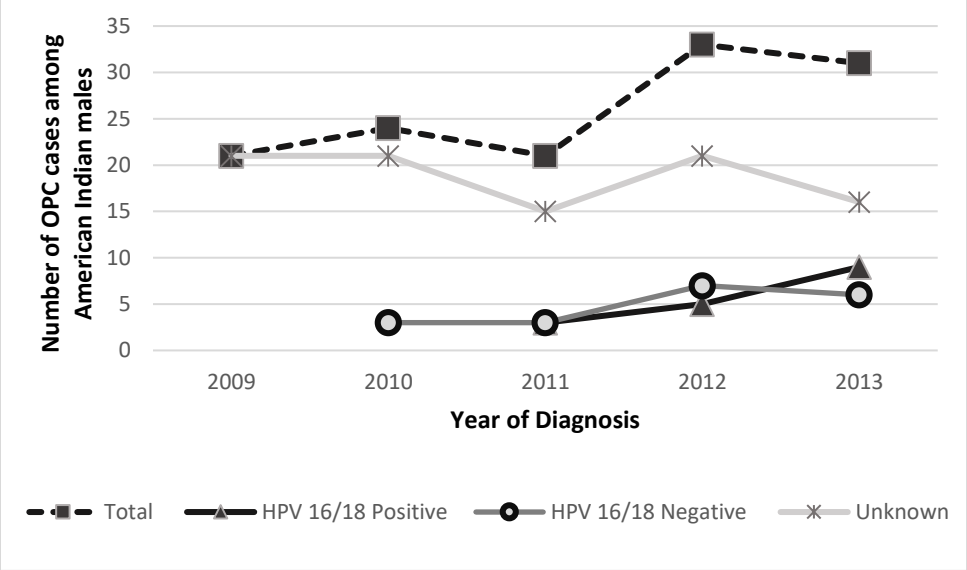
6a) OPCs by HPV status among NHW males



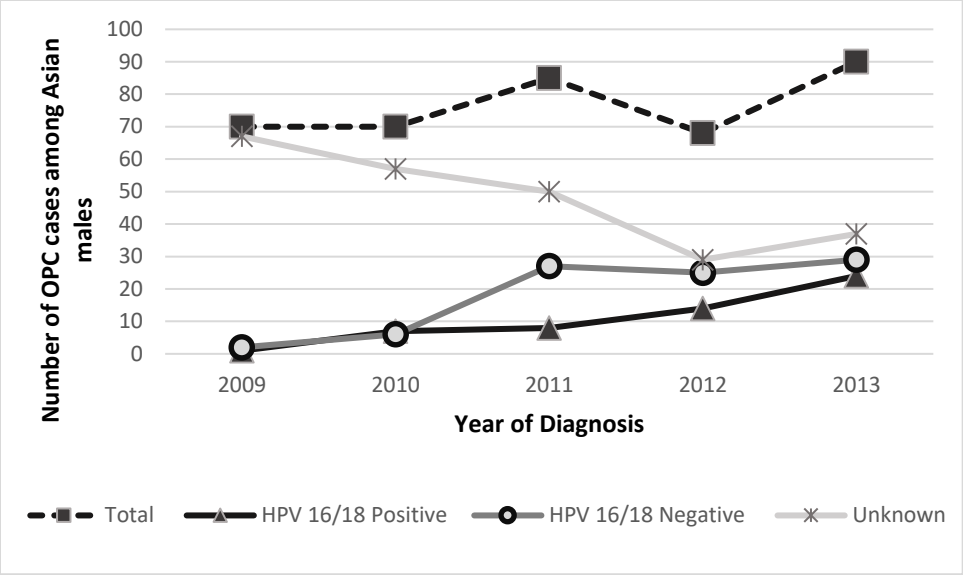
6b) OPCs by HPV status among NHB males



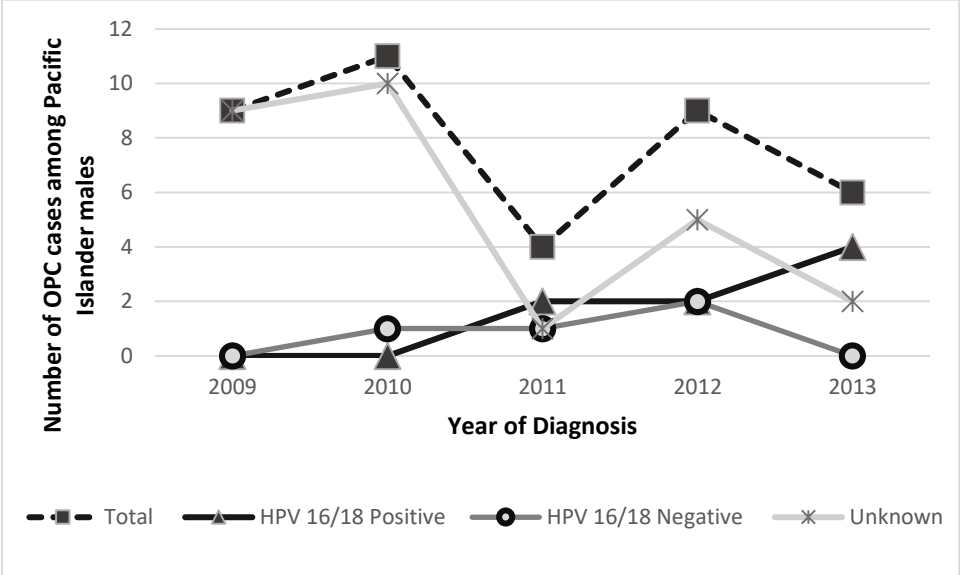
6c) OPCs by HPV status among Hispanic males



6d) OPCs by HPV status among American Indian males



6e) OPCs by HPV status among Asian males



6f) OPCs by HPV status among Pacific Islander males

D. **Discussion**

The findings from our study reveal that there are significant differences in the distribution of site group and subsites by race/ethnicity. Oropharynx was the most common site group for HNSCCs among NHW and American Indian males. However, non-oropharynx (mainly nasopharynx) and oral cavity were the most common site groups for Asians, and larynx was the most common site group for NHB males and Hispanics. Our findings further highlight that these minority groups are not homogeneous and have substantial intra-group differences. Within Asians, only South Asian I/P had very high likelihood for OCC, while the other Asian groups had either comparable or lower proportion of OCC than NHW. This could be due to specific risk factors (such as, areca nut use) that affect oral cavity but not the other HNSCC sites. On the other hand, Chinese had a much higher likelihood of Non-OPC, perhaps due to EBV and other risk factors, such as diet (Jia et al., 2010; McDermott, Dutt, & Watkinson, 2001). This underlines the need for studying subgroups within the minority racial/ethnic groups so that high risk groups, with distinct characteristics and risk factors, can be identified and targeted interventions can be designed. Policy changes that encourage screening and discourage the use of specific risk factors (such as, restricting sale of areca nut, increasing awareness regarding the risk associated with salt-cured foods) should also be considered.

Although there are extremely limited number of studies that have explored HNSCCs in minority groups, our findings are consistent with the few studies that have been published. Our finding of higher nasopharyngeal cancer in Asians are consistent with those reported by Jin et al. (2017) who examined the major cancers among Asian American subgroups in the US. However, they reported lower oral cancer incidence in Asians than NHW. This lower incidence is possibly

due to combining of oral and pharyngeal sites under oral cancer, thereby, blurring the differences by site.

A steep increase in the overall number of cases and OPC cases, in particular (by 83% from 2004 to 2013), was noticed in NHW males. This is consistent with the literature (Chaturvedi et al., 2008; Chaturvedi et al., 2011; Simard et al., 2014) showing a rise in HPV positive OPC cases in NHW males, which has garnered a lot of attention in the recent years. However, our findings suggest a more pronounced concomitant increase in other HNSCCs among minority racial/ethnic groups. The cases of OCC increased by 120% among Asians, OPC cases increased by 121% (and OCC increased by 112%) among American Indians from 2004 to 2013. Consistent with the results of our previous work on HNSCCs in NHW and NHB, where we had found the risk of HPV positive OPCs to be lower in NHB compared to NHW males (Peterson et al., 2016), this study revealed that the HPV 16/18 positive OPCs are less likely in all the minority groups, including NHB.

While HPV 16/18 positive cases increased among all racial/ethnic groups from 2009 to 2013, there was a simultaneous decrease in the number of cases with HPV unknown status largely due to increased testing of OPCs for HPV, therefore, more cases are being diagnosed with HPV positive cancer. This may partly explain the rise in HPV positive OPC cases, reported in many studies; however, actual increase in incidence of HPV positive OPCs could also be playing a role here. Smoking rates have been going down in the US, from 25% in 1997 to 15% in 2015 (CDC, 2017b), thereby, leading to a decrease in smoking associated (HPV negative) HNSCCs (Vigneswaran & Williams, 2014) but smoking and other forms of tobacco use is still an important risk factor, especially for groups in which tobacco use is still high.

In our study, the diagnosis at a younger age range was much more likely among Asian and Pacific Islander males compared to all other racial/ethnic groups, which means that they live longer with complications and impacts of cancer and its treatment. Moreover, these cases were more likely to be HPV negative, thereby suggesting that the risk factors (possibly areca nut use or tobacco use) in these populations debut at a much younger age. Early initiation of areca nut chewing habit at a tender age of 13 – 15 has been reported in young boys in India (Gunaseelan, Shanthi, Sowmya, & Datta, 2007). Even though smoking rates are lower among Asians overall than other racial/ethnic groups in the US (Adams et al., 2016; Martell, Garrett, & Caraballo, 2016), there is a wide variation within the group (Martell et al., 2016). The likelihood of early initiation of smoking is also higher with nearly half of Asian American smokers starting between the age of 18 – 21 years (compared to 40% in Blacks, 38% in Hispanics and 37% in NHW (Trinidad, Gilpin, Lee, & Pierce, 2004).

Although chronic thermal injury from hot tea has been implicated in esophageal cancer (Islami et al., 2020; Lin, S. et al., 2020), similar findings have not yet been reported for HNSCCs. However, the effect of hot tea on HNSCCs in certain minority groups, such as Asian subgroups known to consume hot tea, cannot be completely ruled out while also acknowledging the anti-cancer protective effect of tea that has been reported by some studies (Huang et al., 2014; Zhang, Wendong, Geng, Han, & Dou, 2014). Moreover, the role of oral health beliefs, oral hygiene practices and access to dental care cannot be discounted, especially among minority groups. Prior research has shown higher rates of tooth decay and untreated dental caries, lower dental care and less frequent use of dental services among NHB and Hispanics (Feinberg, 2015; Wu, Liang, Plassman, Remle, & Bai, 2011).

A major strength of this study is that this is the first study to comprehensively explore HNSCCs by site group and HPV status in minority racial/ethnic groups in the US and compare them to NHW males. Previous studies that have examined HNSCCs in minority racial/ethnic groups, have mainly examined NHB (Peterson et al., 2016; Peterson et al., 2017). Few studies that have been done on Hispanics (Oh et al, 2017, Parasher et al, 2014) have not examined HNSCCs by HPV status. Other minority racial/ethnic groups have either not been studied at all or if they have been studied, HNSCCs were a small part of the study. Another major strength of this study is that we used a large national registry which covers more than 70% of the cases in the US from all areas, including Puerto Rico; therefore, we were able to get enough sample for even small minority groups such as Pacific Islanders, allowing us to include them in the analysis.

Our study had some limitations. We were limited in our ability to assess APC for HPV status. Although a large proportion of cases were of unknown HPV status, it was expected as HPV testing is not routinely conducted for all cases. In fact, recommendations for HPV testing of OPCs have only recently been released. The HPV unknowns are more likely to be HPV negative. Therefore, it would be inappropriate to calculate APCs by just including the cases with known HPV status because they may have been tested because of suspicion of HPV positivity. Another limitation is that we did not have data on the country of birth (foreign born/US born).

E. **Conclusion**

Certain minority racial/ethnic groups in the US are estimated to become the majority groups in the near future. Asians are the fastest growing minority racial/ethnic group, followed by Hispanics. Although all the minority groups are more likely to be diagnosed with Non-OPC than NHW, Asians have the highest odds among all. Asians also have the highest odds of being

diagnosed with OCC and laryngeal cancer, compared to NHW. They are also less likely to be HPV 16/18 positive, which tends to have better prognosis. Therefore, Asian population needs to be examined further to identify high risk subpopulations and their corresponding risk factors, and to assess survival.

V. HEAD AND NECK SQUAMOUS CELL CARCINOMAS AMONG MALES OF THREE LARGEST ASIAN DIASPORAS IN THE US, 2004 - 2013

A. Introduction

Head and neck cancers are the sixth most common type of cancers in the world (Vigneswaran & Williams, 2014); however, there is tremendous geographic variation across the globe. Approximately 58% of the global HNSCC cases occur in Asia alone (Kulkarni, 2013), and a large proportion of these are from South Asia. It is known that OCC is the most common cancer in males in South Asian countries like India, Pakistan and Sri Lanka (Warnakulasuriya, 2009). Thirty percent of all cancer cases in males in India (Kulkarni, 2013) and 21% of all cancer cases in males in Pakistan (Bhurgri et al., 2006; Joshi et al., 2014) are head and neck cancers. Such high rates are attributed to the use of smokeless tobacco and areca nut (Khan et al., 2014). Similarly, incidence of nasopharyngeal cancer is higher in China. While nasopharyngeal cancer is considered a rare disease in most of the world, it is the 11th most common cancer in China (Cao et al., 2011). In certain parts of Southern China, the incidence is up to 20 -50 times higher than the global average (Jia et al., 2006; Jia et al., 2010). The main causes for this malignancy are EBV infection, smoking, alcohol use and dietary patterns, such as salted fish and cured foods consumption (Jia et al., 2010; McDermott et al., 2001). Similarly, head and neck cancers have the third highest incidence among all cancers in Philippines (Department of Health, Republic of the Philippines, 2019).

When we contrast these Asian countries to the US, HNSCCs represent less than six percent of all new cancer diagnoses among males (based on estimated new cases in 2018) (American Cancer Society, 2018) making it the eighth most common cancer among males in the US (Siegel et al., 2019; Vigneswaran & Williams, 2014).

According to the US Census Bureau, Chinese, Asian Indian and Filipino are the three largest Asian groups in the US. In 2017, there were 5 million Chinese, 4.9 million South Asians of Indian and Pakistani origin (4.4 million of these are Asian Indian alone) and 4 million Filipinos, who together accounted for more than 62% of the total Asian population in the US (US Census Bureau, 2019). Asian population increased by 88% from 2000 to 2017, making it the fastest growing population among all racial/ethnic groups. Among Asian Indians, the percentage increase was 131%, while it was 85% for Chinese and 67% for Filipinos from 2000 to 2017 (based on the population reported in US Census (Barnes & Bennett, 2002) and American Community Survey (US Census Bureau, 2019)). This growth is largely attributed to immigration, with Chinese and Asian Indians among the top three groups immigrating to the US. These two groups were just behind Mexicans in receiving lawful permanent residence in the US (US Department of Homeland Security, 2019). The high immigration rate from Asian countries suggests that the head and neck cancer rates and patterns seen in these countries could potentially be of concern in these diasporas in the US. However, the risk of HNSCCs in these Asian diasporas living in the US is unknown. The rates reported for Asians as a group do not show the complete picture as Asians are not homogeneous (Chen Jr et al., 2006). Apart from the cultural, genetic and other differences among Asians, it is important to note that the baseline rates in various Asians countries are not same.

Studies from UK and Australia have shown that South Asian diaspora has higher rates of head and neck cancers than the general population of these countries (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004; McCredie et al., 1999; Moles et al., 2008; Warnakulasuriya et al., 1999; Warnakulasuriya et al., 2002), and that these populations continue the high risk behaviors (such as, areca nut use) post migration (Ahluwalia, 2005).

Similar studies have not been done in the Asians living in the US. Studies have also shown that the risk of nasopharyngeal cancer continues to be higher in Chinese even after they migrate to other countries (McCredie et al., 1999; Warnakulasuriya et al., 1999).

The purpose of this study was to examine the characteristics, such as site group and stage at diagnosis, of male HNSCC cases among three largest Asian subpopulations in the US and compare them to NHW. The secondary purpose was to explore the temporal trends by site group and subsite. We hypothesized that in comparison to NHW, OCC will be more common in South Asian I/P while non-OPC (mainly nasopharyngeal cancer) will be higher in Chinese. As Asians are likely to have lower screening rates and lower awareness of screening, we hypothesized that they will have more advanced stage at diagnosis. Studying Asian diasporas in America and comparing them to NHW will provide a new perspective on how Asians immigrating to developed countries fare in terms of HNSCCs. The conceptual framework for the association of race/ethnicity with HNSCC site group was presented in Figure 1 in Chapter III. The conceptual framework for the association of race/ethnicity with HNSCC stage at diagnosis is presented below in Figure 7.

B. **Methods**

1. **Study population**

Data from NCDB were used for studying HNSCCs among males in the three largest Asian subpopulations in the US, including Chinese, South Asian I/P, and Filipinos (US Census Bureau, 2017), and compare them to NHW. Other South Asian groups, such as Bangladeshi and Sri Lankans, could not be included as they were not reported separately in NCDB. The sample selection flowchart for the main analysis is presented below in Figure 8.

Figure 7: Conceptual framework for the association of race/ethnicity with HNSCC stage at diagnosis

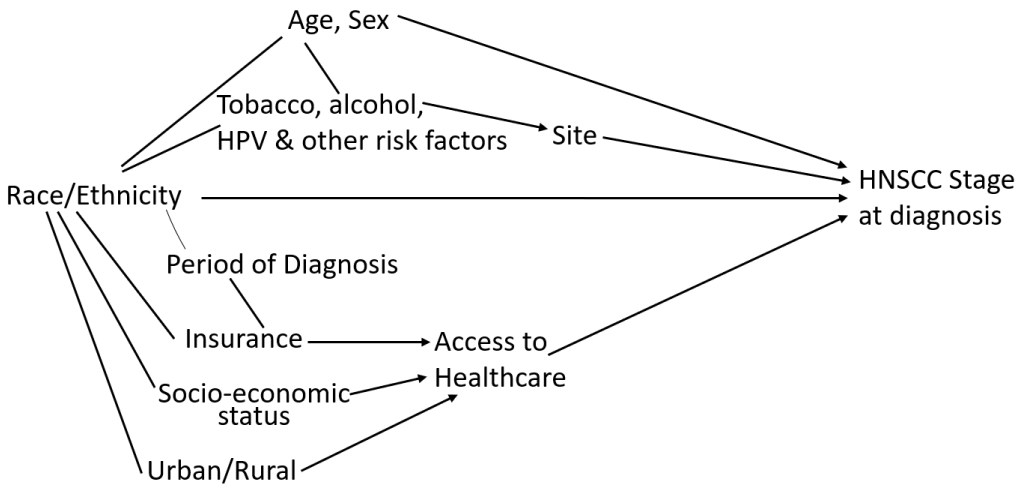
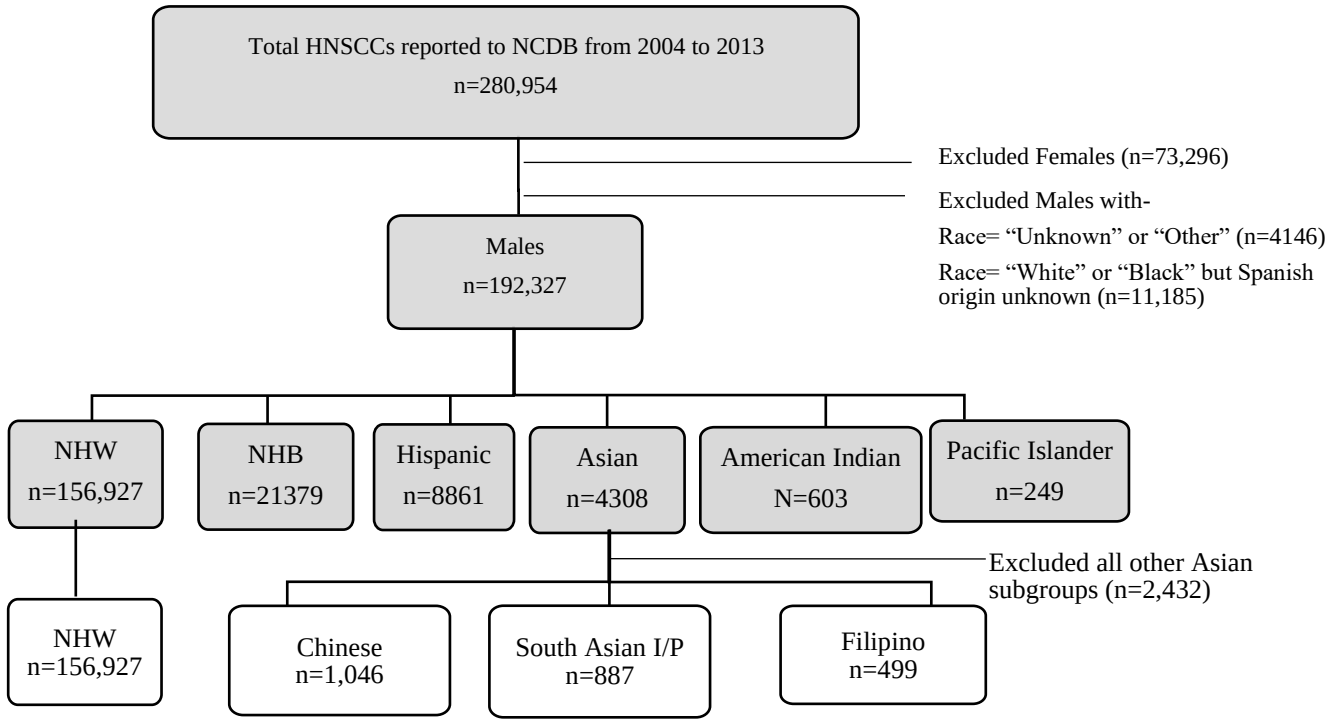


Figure 8: Flowchart of the study population and the sample size



For the analysis of late stage diagnosis, we excluded cases diagnosed at stage 0 (n=4,864), as it represents "carcinoma-in-situ", and stage not applicable or unknown (n=12,977). Therefore, the sample was reduced to 884 (0.6%) Chinese, 811 (0.6%) South Asian I/P, 427 (0.3%) Filipino and 139,396 (98.5%) NHW males.

2. Variables

a. Exposure Variable – Race/Ethnicity

Self-reported race/ethnicity was categorized as Chinese, South Asian I/P, Filipino and NHW. South Asian subgroup was created by combining "Asian Indian", "Pakistani" or "Asian Indian or Pakistani" racial categories provided in the NCDB (Other South Asian groups could not be included as they were not listed under racial categories in NCDB). Those who identified themselves as "Chinese" or "Filipino" were included in the Chinese and Filipino subgroup, respectively. These Asian groups were to be compared to NHW; therefore, NHW were included as the referent group. All those who reported their race as "White" and ethnicity as "Non-Spanish; non-Hispanic" were included under NHW.

b. Outcome Variables and Other Clinical Variables

The main outcome of the analysis was site group. Site group includes oral cavity, oropharynx, non-oropharynx and larynx. Oral Cavity includes lips, anterior tongue, gums, buccal mucosa, hard palate, and other mouth; oropharynx includes base of tongue and tonsils besides oropharynx; non-oropharynx includes nasopharynx, hypopharynx and other pharynx (Peterson et al., 2016; Piccirillo et al., 2007).

The secondary outcome of this analysis was late stage diagnosis where late stage refers to stage III-IV and early stage refers to stage I-II. (Carvalho, André L. et al., 2002; Murphy

et al., 2016) The overall American Joint Committee on Cancer (AJCC 6th and 7th edition) stage at diagnosis, taken from pathologic stage group (39%) and if pathologic stage not reported then clinical stage group (61%), was classified as Stage 0, I, II, III and IV. Apart from these variables, HPV status was categorized as HPV 16/18 positive (i.e., positive for type 16, type 18 or both), HPV 16/18 negative (i.e., negative for type 16 and 18 but could be positive for other HPV types), and HPV status unknown. More details on categorization of HPV status are included in Chapter III. To account for the effect of comorbidities on stage at diagnosis (Gurney, Sarfati, & Stanley, 2015), Charlson/Deyo score was included in the analysis. Charlson/Deyo score, representing the severity of comorbidities, was categorized as: 0 (i.e., either no comorbidities, or have a comorbidity that is not included in the Charlson Comorbidity Score Mapping), 1 and ≥2.

c. **Demographic Variables**

To fully account for differences by age, age at diagnosis was categorized as <40, 41-50, 51-60, 61-70, 70+(Murphy et al., 2016) Due to the small number of cases less than 30 years of age, less than 40 years was used as the lowest age group. Insurance status was categorized as Uninsured, Medicaid, Medicare, Other Government and Private. For assessing effect modification with race/ethnicity, the Other Government insurance category was excluded due to extremely low sample size in certain Asian subgroups. To account for the impact of year of diagnosis, especially on stage at diagnosis, the study period was broken down into two categories based on the landmark Affordable Care Act (Pre-ACA 2004-2010, and Post-ACA 2011-2013) as these two time periods may be different in terms of patients' access to care. Area-level economic advantage has been linked to certain HNSCCs (Peterson et al., 2017); therefore, two area-level variables, education (percentage of adults without high school diploma in patient's zip code) and income (median household income in patient's zip code), based on the

2012 US census, were categorized as quartiles and were included in the analysis as proxies for individual level SES. Rurality of residence can potentially affect a person's exposure to certain risk factors and can also influence access to care, thereby, affecting the stage at diagnosis. Therefore, rural region of residence was included in the analysis. More details on this variable are included in Chapter III.

d. **Institutional Variables**

To account for the geographic differences in distribution of racial/ethnic groups, site group of cancer, and institutionalized discrimination affecting stage at which medical care was sought, geographic area of the reporting facility was included in the analysis. It was categorized into four areas: Midwest, Northeast, South and West. The type of facility was classified as Academic/Research Program, Community Cancer Program, or Integrated Network Program (Other specified types of cancer programs category was excluded because there was only one Filipino case and zero cases for Chinese and South Asians reported under this category in NCDB). Since longer travel distance can impact the stage at which medical care was sought, estimated patient travel distance which represents the distance between the centroids of the reporting hospital's zip code and a patient's residential zip code was used to create a categorical travel distance variable with values <12.5, 12.5 to <50, 50 to <250 miles. (Massarweh et al., 2014, Ryan et al., 2018).

3. **Statistical Analyses**

a. **Distribution of Various Characteristics by Race/Ethnicity**

Univariate analyses were performed to examine the distribution of variables and the proportion of missing observations. Bivariate analysis was done to examine the distribution

of various demographic (including age, insurance status, region of residence, area-level education and area-level income), clinical (including site group, subsite, stage, HPV status) and institutional variables (such as type of facility, geographic area of reporting facility and distance from the facility) by race/ethnicity. One-way ANOVA was used to assess the difference in mean age among racial/ethnic groups. As travel distance (distance between patient residence and the reporting hospital) was non-normally distributed, Kruskal-Wallis test was used to assess difference in means. Chi square test was used to assess racial/ethnic differences in the distribution of categorical variables.

b. **Assessing the Association of Race/Ethnicity with Site Group**

Bivariate associations were examined between site group and all other potential predictors including race/ethnicity (Conceptual model in Figure 1 under Chapter III). Although stratified analysis was conducted to assess interactions of race/ethnicity with other independent variables (including age, area-level income, and area-level education) that were selected *a priori* based on conceptual understanding, the final results presented here are not stratified because of complexity in interpretation of results and loss of clinical relevance due to multiple strata for each racial group (leading to up to 12 comparisons for race/ethnicity with site group). Race/ethnicity (as the main exposure) along with all other potential predictors of site group identified with the conceptual model (Figure 1) were included in the initial multinomial logistic model. Manual backward selection was then used to obtain a final model that would provide measure of association (OR) with 95% confidence intervals (CI). Confounding was assessed by dropping the variables one at a time from the model to assess whether there was a change in exposure level ORs, keeping the sample size constant. Geographic area of reporting facility was found to be a confounder in the model, because dropping it out changed at least one of the

exposure level ORs by ≥10%. Age at diagnosis and area level education were kept in the final model because they are strong conceptual confounders and they improved the AIC (i.e., AIC was lower) when included in the model. For comparison, another model was run by adding all the conceptual confounders initially identified, although they did not appreciably alter the association between race/ethnicity and site group in the model.

c. **Assessing the Association of Race/Ethnicity with Late Stage Diagnosis**

Bivariate associations were examined between late stage and all other potential predictors including race/ethnicity (conceptual model in Figure 7). Although stratified analysis was conducted to explore potential interactions of race/ethnicity with conceptual effect modifiers (including site group, insurance status, area-level education, and area-level income) selected *a priori*, the final results were not stratified because of complexity in interpretation and applicability of results and loss of clinical relevance. Initial multinomial logistic model included all the predictors of late stage at diagnosis, identified from the conceptual model. Manual backward selection was used to obtain a final model. Site group was the only confounder in the model as it changed the exposure level ORs by ≥10%; however, additional variables were retained in the model because they were strong conceptual confounders (age, insurance and area-level education). Moreover, retaining them in the model reduced AIC, thereby, improving the fit of the model.

d. **Examining Temporal Trends**

Temporal trends in HNSCC cases for site groups and subsites were assessed by calculating APC. APC were “calculated by fitting a least squares regression line to the natural logarithm” of annual rates (NCI SEER, n.d.). The annual rates were calculated by dividing the

number of cases of HNSCC of a particular site by the total number of annual HNSCC cases for that subpopulation (Peterson et al., 2016). Data were analyzed using SAS 9.4 (SAS Institute, Cary NC). Microsoft excel was used for creating graphs for trends.

C. **Results**

During the study period (2004 to 2013), 1046 (0.7%) Chinese, 887 (0.6%) South Asian I/P, 499 (0.3%) Filipinos, and 156,927 (98.4%) NHW males were diagnosed with HNSCC. Although the mean age at diagnosis for all three Asian subpopulations was between one to three years lower than that in NHW ($p<0.001$, Table VII), there was a striking difference at the lower end of age categories as the proportion of cases diagnosed by the age of 40 years was far greater in all three Asian subpopulations (Chinese 14%, South Asian I/P 10% and Filipino 8%) compared to NHW (<3%) ($p<0.0001$), which also corresponds to the smaller proportion of Asian cases with Medicare insurance. The Asian subpopulations also had a slightly larger proportion of cases with private insurance (Filipinos 55%, South Asian I/P 52% and Chinese 50% vs. NHW 47%) and larger proportion enrolled into Medicaid (Chinese 19%, South Asian I/P 15% and Filipino 13% vs. NHW 8%). South Asian I/P were more likely to be uninsured than NHW (12% vs. 6%, $p<0.001$).

The Asian subpopulations were less likely to live in zip code areas with lower median household income compared to NHW ($p<0.0001$). Chinese (36%) were most likely, followed by Filipinos (26%) to be from lowest area-level education quartile, compared to NHW (15%). There were tremendous geographic variations, with most of the Filipino cases (71%) and Chinese cases (55%) reported from facilities in West, while most of the South Asian I/P cases (38%) were

TABLE VII

COMPARISON OF PATIENT CHARACTERISTICS IN CHINESE, SOUTH ASIAN I/P[a] AND FILIPINO MALES IN THE US WITH NHW MALES, 2004 – 2013

	Chinese males N=1046	South Asian I/P males N=887	Filipino males N=499	NHW males N=156927	p-value
	Mean [SD] or n (%)	Mean [SD] or n (%)	Mean [SD] or n (%)	Mean [SD] or n (%)	
Age at diagnosis					
Mean years [SD]	57.1 [14.6]	57.7 [13]	59.8 [13.2]	61 [11]	<0.0001
Age group					
≤40	144 (13.8%)	88 (9.9%)	41 (8.2%)	4009 (2.6%)	<0.0001
41-50	201 (19.2%)	164 (18.5%)	80 (16.0%)	22852 (14.6%)	
51-60	286 (27.3%)	261 (29.4%)	139 (27.9%)	53306 (34.0%)	
61-70	205 (19.6%)	210 (23.7%)	127 (25.4%)	44806 (28.6%)	
>70	210 (20.1%)	164 (18.5%)	112 (22.4%)	31954 (20.4%)	
Period of Diagnosis					<0.0001
Pre ACA (2004-10)	524 (59.1%)	714 (68.3%)	335 (67.1%)	103468 (65.9%)	
Post ACA (2011-13)	363 (40.9%)	332 (31.7%)	164 (32.9%)	53459 (34.1%)	
Insurance [b]					<0.0001
Private	507 (50.0%)	447 (52.4%)	265 (54.9%)	71180 (46.9%)	
Other Govt	6 (0.6%)	1 (0.1%)	15 (3.1%)	3782 (2.5%)	
Medicare	250 (24.6%)	176 (20.6%)	108 (22.4%)	55382 (36.5%)	
Medicaid	192 (18.9%)	125 (14.6%)	61 (12.6%)	12576 (8.3%)	
No Insurance	60 (5.9%)	104 (12.2%)	34 (7.0%)	8959 (5.9%)	
Area-level Median Household Income [c]					<0.0001
$63,000+	496 (47.8%)	468 (54.1%)	265 (53.8%)	46195 (29.9%)	
$48,000-$62,999	225 (21.7%)	202 (23.4%)	135 (27.4%)	42688 (27.6%)	
$38,000-$47,999	188 (18.1%)	125 (14.4%)	62 (12.6%)	39764 (25.8%)	
<$38,000	129 (12.4%)	70 (8.1%)	31 (6.3%)	25731 (16.7%)	
Area-level educational attainment (% with No HSD) [d]					<0.0001
<7%	200 (19.3%)	261 (30.1%)	66 (13.4%)	35794 (23.2%)	
7-12.9%	262 (25.2%)	262 (30.2%)	153 (31.0%)	52573 (34.0%)	
13-20%	206 (19.8%)	186 (21.5%)	146 (29.6%)	42266 (27.4%)	
>=21%	370 (35.6%)	157 (18.1%)	128 (26.0%)	23839 (15.4%)	
Rural Residence [e]					<0.0001
Yes	3 (0.3%)	8 (0.9%)	14 (2.9%)	10371 (6.8%)	
No	1017 (99.7%)	840 (99.1%)	475 (97.1%)	141163 (93.2%)	
Geographic location of the reporting facility [f]					<0.0001
Midwest	52 (5.7)	156 (19.4)	38 (8.2)	40489 (26.4)	
North East	295 (32.2)	305 (37.9)	57 (12.3)	29278 (19.1)	
South	65 (7.1)	234 (29.1)	42 (9.1)	60945 (39.7)	
West	503 (55.0)	110 (13.7)	327 (70.5)	22887 (14.9)	

TABLE VII (Continued)

COMPARISON OF PATIENT CHARACTERISTICS IN CHINESE, SOUTH ASIAN I/P[a] AND FILIPINO MALES IN THE US WITH NHW MALES, 2004 – 2013

	Chinese males N=1046	South Asian I/P males N=887	Filipino males N=499	NHW males N=156927	p-value
	Mean [SD] or n (%)	Mean [SD] or n (%)	Mean [SD] or n (%)	Mean [SD] or n (%)	
Type of facility					<0.0001
Academic/research	459 (50.2)	520 (64.6)	201 (43.4)	64650 (42.1)	
Community cancer	102 (11.2)	53 (6.6)	56 (12.1)	16591 (10.8)	
Comprehensive Com	228 (24.9)	194 (24.1)	190 (41.0)	63047 (41.1)	
Integrated Network	126 (13.8)	38 (4.7)	16 (3.5)	9258 (6.0)	
Estimated travel distance to reporting facility [g]					<0.0001
<12.5	862 (83.5)	519 (60.6)	379 (77.7)	76762 (50.5)	
12.5 to <50	145 (14.0)	292 (34.1)	96 (19.7)	54874 (36.1)	
50 to <250	25 (2.4)	46 (5.4)	13 (2.7)	20470 (13.5)	

[a] South Asian I/P refers to Asian Indian and Pakistani.

[b] Represents primary payer at diagnosis.

[c] Based on 2012 American Community Survey (2008-2012, adjusted for 2012 inflation) median household income in the patient's zip code area.

[d] Based on 2012 American Community Survey (2008-2012) percentage of adults without high school diploma in patient's zip code area.

[e] Rurality and urban influence is based on adjacency to metro area determined by matching the patients' area (state and county) FIPS code (recorded at the time of diagnosis) against 2003 USDA Economic Research Service. Rural areas include those that were completely rural counties non-adjacent to a metro area or urban population (of any size) non-adjacent to a metro area. Urban includes counties in metro areas (of any population size) or urban population (of any size)/completely rural population adjacent to a metro area (USDA Economic Research Service, 2004)

[f] Midwest represents Ohio, Michigan, Indiana, Wisconsin, Illinois, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska and Kansas. North East represents Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey and Pennsylvania. South includes Delaware, District of Columbia, Maryland, Virginia, West Virginia, Kentucky, North Carolina, South Carolina, Tennessee, Georgia, Florida, Alabama, Mississippi, Arkansas, Louisiana, Texas and Oklahoma. West includes Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, California, Oregon, Washington, Alaska and Hawaii (US Census Bureau, n.d.).

[g] Estimated travel distance represents the distance between the centroids of the reporting hospital's zip code and a patient's residential zip code

reported from North East. South Asian I/P were most likely to be diagnosed at an Academic/Research facility compared to NHW (65% vs. 42%, $p<0.0001$). Asian subgroups were also more likely to have lower estimated travel distance to reporting facility than NHW ($p<0.0001$).

While South Asian I/P had higher proportion of OCC (59% vs. 25% in NHW, $p<0.001$), Chinese and Filipinos were more likely to have non-OPC (which includes nasopharynx, hypopharynx and other pharynx) (64% and 47%, respectively, vs. 9% in NHW) (Figure 9a). Among OPCs, Chinese (11.7%) and NHW (11.8%) had similar proportion of HPV 16/18 positive cases. Although Filipinos had the lowest proportion of OCC cases, they were the only group where late stage OCC diagnosis was more common than early stage OCC diagnosis. Among all site groups, OPCs and Non-OPCs had a much higher likelihood of late stage diagnosis (four to eight times higher) across all three Asian groups as well as NHW. (Fig. 9b).

Nearly 36% (318/887) of all HNSCCs and 60% (318/525) of all OCCs among South Asian I/P were situated in gums, floor of mouth and buccal mucosa; with buccal mucosa (ICD code C060) alone contributing 142 cases. The higher proportion of non-OPC in Chinese and Filipinos was due to nasopharyngeal cancer, which is the most common HNSCC in these subgroups, accounting for 60% of all HNSCCs in Chinese and 41% of all HNSCCs in Filipinos. Diagnosis at advanced stage (Stage III/IV) was more likely in Filipinos. The proportion of HPV16/18 positive OPCs in Chinese was similar to that of NHW. The other two Asian groups had a lower proportion of HPV 16/18 positive OPCs. South Asian I/P (followed by Filipinos) were more likely to have unknown HPV status in this cohort. A greater proportion of Chinese had a lower comorbidity score compared to the other groups suggesting that they were generally healthier than other groups (Table VIII).

Figure 9: Distribution of HNSCC cases among males of three largest Asian groups in the US in comparison to NHW by site grouping (a), and by site group and stage at diagnosis (b)

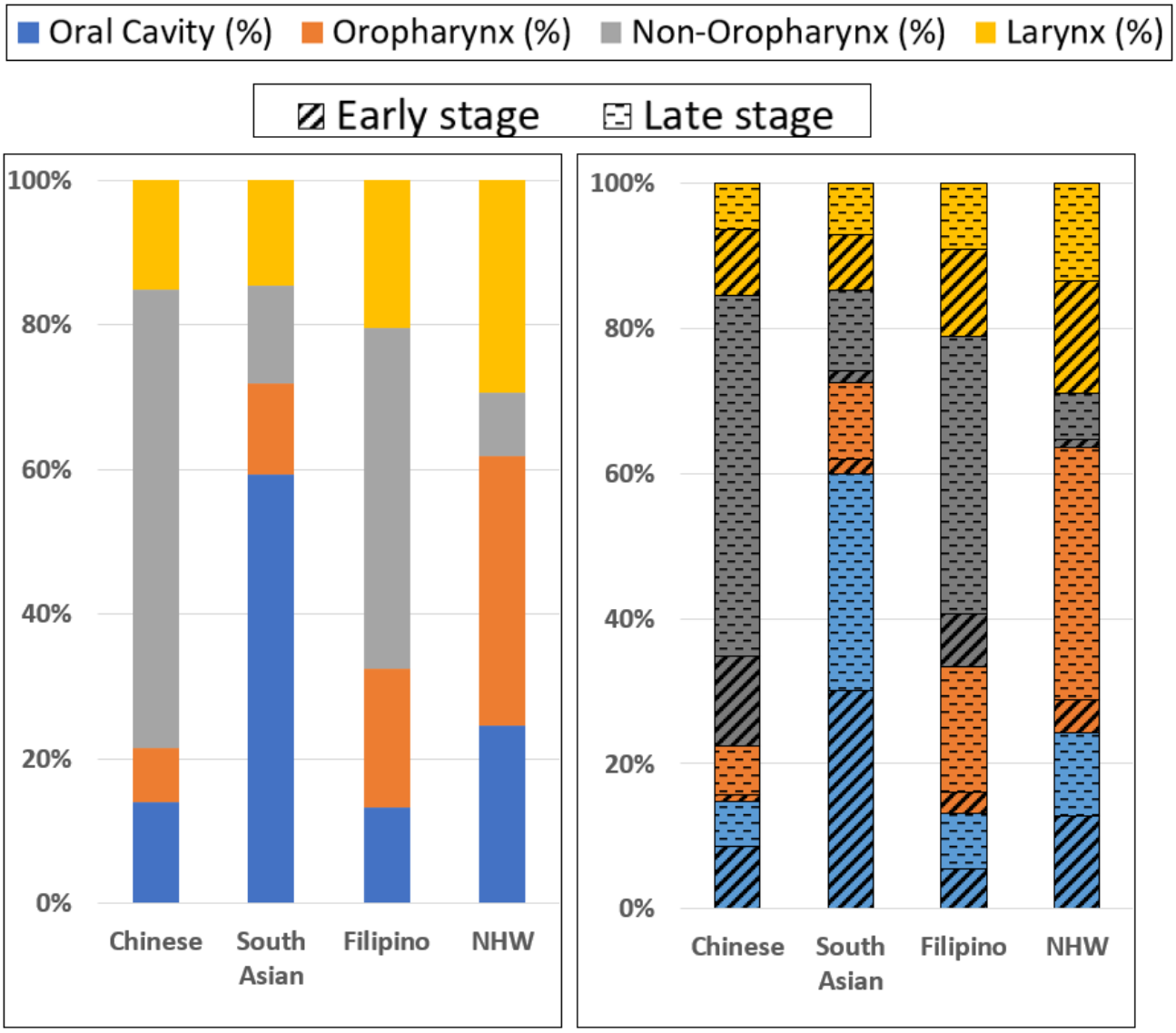


TABLE VIII

CLINICAL CHARACTERISTICS AMONG MALES OF CHINESE, SOUTH ASIAN I/P AND FILIPINO ORIGIN IN COMPARISON TO NON-HISPANIC WHITES IN THE US

	Chinese males (N=1046) n (%)	South Asian I/P males (N=887) n (%)	Filipino males (N=499) n (%)	Non-Hispanic White males (N=156927) n (%)	p-value
Site Group					<0.0001
Oral Cavity	147 (14.1)	525 (59.2)	66 (13.2)	38585 (24.6)	
Oropharynx	77 (7.4)	112 (12.6)	96 (19.2)	58502 (37.3)	
Non-Oropharynx	664 (63.5)	121 (13.6)	235 (47.1)	13631 (8.7)	
Larynx	158 (15.1)	129 (14.5)	102 (20.4)	46209 (29.4)	
Primary anatomical subsite					<0.0001
Lip	1 (0.1)	12 (1.4)	2 (0.4)	5147 (3.3)	
Gum/FOM/ otherM	61 (5.8)	318 (35.8)	38 (7.6)	18702 (11.9)	
Tongue (Anterior)	85 (8.1)	195 (22.0)	26 (5.2)	14736 (9.4)	
Tongue (Base)	23 (2.2)	51 (5.8)	31 (6.2)	24295 (15.5)	
Tonsil	42 (4.0)	43 (4.8)	54 (10.8)	28313 (18.0)	
Oropharynx	12 (1.2)	18 (2.0)	11 (2.2)	5894 (3.8)	
Nasopharynx	630 (60.2)	67 (7.6)	205 (41.1)	4194 (2.7)	
Hypopharynx	31 (3.0)	49 (5.5)	23 (4.6)	7511 (4.8)	
Other Pharynx	3 (0.3)	5 (0.6)	7 (1.4)	1926 (1.2)	
Larynx	158 (15.1)	129 (14.5)	102 (20.4)	46209 (29.4)	
AJCC[a] Stage of Diagnosis					<0.0001
0	15 (1.4)	12 (1.4)	7 (1.4)	4830 (3.1)	
I	169 (16.2)	207 (23.3)	64 (12.8)	29998 (19.1)	
II	107 (10.2)	128 (14.4)	55 (11.0)	17408 (11.1)	
III	237 (22.7)	117 (13.2)	87 (17.4)	24753 (15.8)	
IV	371 (35.5)	359 (40.5)	221 (44.3)	67237 (42.8)	
NA/Unk	147 (14.0)	64 (7.2)	65 (13.0)	12701 (8.1)	
HPV status (among OPC cases, 2009-2013)					0.15
HPV 16/18 negative	12 (26.1)	14 (19.2)	13 (25.5)	7787 (22.7)	
HPV 16/18 positive	9 (19.6)	7 (9.6)	6 (11.8)	6889 (20.1)	
HPV unknown	25 (54.4)	52 (71.2)	32 (62.8)	19591 (57.2)	
HPV status (among OPC cases, 2009-2013)					0.0089
HPV (all) negative	10 (21.7)	12 (16.4)	6 (11.8)	3850 (11.2)	
HPV 16/18 positive	9 (19.6)	7 (9.6)	6 (11.8)	6889 (20.1)	
HPV other HR positive	2 (4.4)	1 (1.4)	5 (9.8)	1579 (4.6)	
HPV LR positive	0	1 (1.4)	2 (3.9)	2358 (6.9)	
HPV unknown	25 (54.4)	52 (71.2)	32 (62.8)	19591 (57.2)	
Charlson/Deyo comorbidity score					<0.0001
0	924 (88.3)	686 (77.3)	403 (80.8)	125903 (80.2)	
1	108 (10.3)	167 (18.8)	79 (15.8)	24014 (15.3)	
≥2	14 (1.3)	7010 (4.5)	17 (3.4)	7010 (4.5)	

[a] AJCC 6th and 7th edition (Edge & Compton, 2010). Note: AJCC 8th edition came into effect in 2018 and classifies HPV positive OPC as a separate entity with revised staging system (other HPV positive HNSCCs have not yet been separated in AJCC) (Davidson et al., 2018; Lydiatt, O'Sullivan, & Patel, 2018). AJCC 8th edition groups pharynx as: EBV(+/-) nasopharynx, HPV(-) oropharynx and hypopharynx, HPV(+) oropharynx (American College of Surgeons, 2018).

1. **Race/Ethnicity and Site Group**

The Asian subgroups had significantly higher likelihood for Non-OPC (vs. OPC) compared to NHW, but the strongest association was in Chinese ($OR_{adj=}$ 34.0; 95% CI: 26.5 – 43.6), followed by Filipinos ($OR_{adj=}$ 10.0; 95% CI: 7.8 – 12.9), after adjusting for age at diagnosis, area-level education and geographic area of facility. For OCC (vs. OPC), both South Asians and Chinese had a significant association, but it was much stronger in South Asians ($OR_{adj=}$ 7.3; 95% CI: 5.9 – 9.0). Table IX shows the crude and adjusted results for the association of race/ethnicity with site group.

TABLE IX

CRUDE AND ADJUSTED ODDS RATIOS FOR THE ASSOCIATION OF RACE/ETHNICITY WITH SITE GROUPS.

Oral Cavity vs. Oropharynx			
	Crude OR (95% CI)	**Adjusted OR[a] (95% CI)**	**Adjusted OR[b] (95% CI)**
Race/Ethnicity			
Chinese	**2.89 (2.19 – 3.81)**	**3.12 (2.34 – 4.15)**	**3.15 (2.35 – 4.22)**
Filipino	1.04 (0.76 – 1.43)	1.07 (0.77 – 1.48)	1.12 (0.80 – 1.57)
South Asian	**7.11 (5.79 – 8.72)**	**7.28 (5.86 – 9.04)**	**7.57 (6.06 – 9.45)**
NHW	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non-Oropharynx vs. Oropharynx			
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	
Race/Ethnicity			
Chinese	**36.96 (29.18 – 46.83)**	**34.00 (26.50 – 43.62)**	**35.01 (27.15 – 45.15)**
Filipino	**10.51 (8.28 – 13.33)**	**10.04 (7.81 – 12.91)**	**11.18 (8.63 – 14.50)**
South Asian	**4.64 (3.58 – 6.00)**	**4.61 (3.50 – 6.07)**	**4.50 (3.38 – 5.99)**
NHW	1.00 (reference)	1.00 (reference)	1.00 (reference)
Larynx vs. Oropharynx			
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	
Race/Ethnicity			
Chinese	**2.60 (1.98 – 3.41)**	**3.10 (2.33 – 4.11)**	**3.22 (2.41 – 4.30)**
Filipino	**1.34 (1.02 – 1.78)**	**1.60 (1.20 – 2.14)**	**1.80 (1.34 – 2.43)**
South Asian	**1.46 (1.13 – 1.88)**	**1.65 (1.27 – 2.15)**	**1.60 (1.22 – 2.12)**
NHW	1.00 (reference)	1.00 (reference)	1.00 (reference)

[a] Adjusted for age at diagnosis, geographic area of facility and area level education.

[b] In addition to variables in model[a], also adjusted for period of diagnosis, rural residence, insurance and area-level income.

2. **Race/Ethnicity and Stage of Cancer**

The crude association of race/ethnicity with late stage diagnosis was significant in South Asian I/P only, with South Asians having lower odds of late stage diagnosis. However, this association did not persist when adjusted for covariates including age at diagnosis, site group, insurance and area level education. After adjustment, only Chinese had significantly lower odds of late stage diagnosis (OR_{adj}=0.7; 95% CI 0.6 – 0.9) compared to NHW, while no difference was found for the other two Asian subgroups (Table X).

3. **Temporal Trends**

At the start of the study period (2004), Chinese had higher number of cases than the other Asian subgroups; however, by 2011 the number of South Asian I/P cases surpassed Chinese. Moreover, there appears to be a gradual increase in the number of cases in South Asians I/P from 65 cases in 2004 to 131 cases in 2013 (Figure 10).

In South Asian I/P males, OCC was the predominant HNSCC site group and there was a substantial increase in the number of cases from 34 in 2004 to 86 in 2013 (APC=1.2, p=0.27) (Figure 11a). When we further look into subsites, this increase in OCC was largely attributable to gum, floor of mouth, other mouth (APC= 3.9, p=0.0895) (Figure 11b).

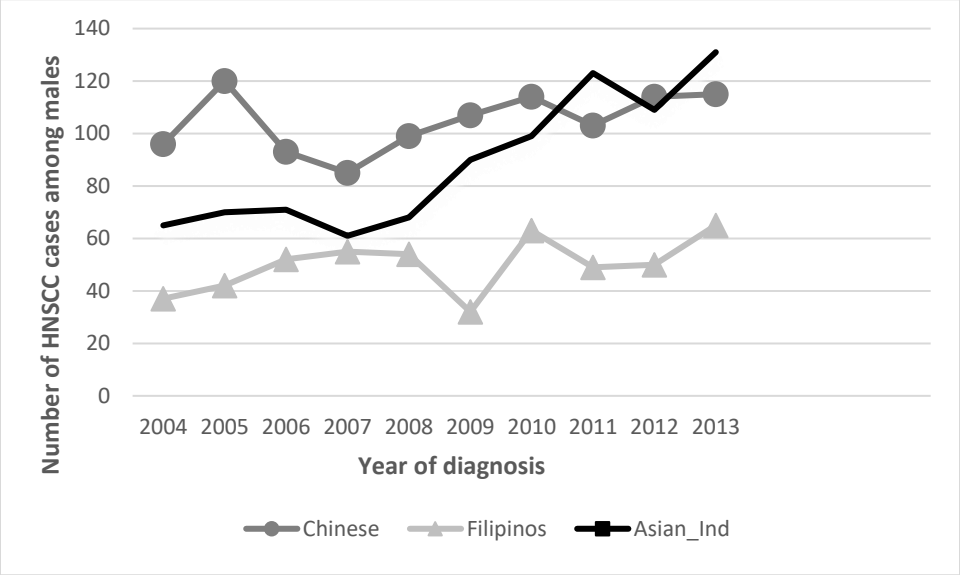
TABLE X

ASSOCIATION OF RACE/ETHNICITY AND OTHER INDEPENDENT PREDICTORS WITH STAGE OF DIAGNOSIS. LATE STAGE DIAGNOSIS REPRESENTS STAGE III-IV AND EARLY STAGE REPRESENTS STAGE I-II.

	Late Stage N=93382 n (row %)	**Early Stage N=48136** n (row %)	**Crude OR (95% CI)**	**Adjusted OR (95% CI)** [a]
Race/Ethnicity				
NHW	91990 (66.0)	47406 (34.0)	1.00 (reference)	1.00 (reference)
Chinese	608 (68.8)	276 (31.2)	1.14 (0.98 – 1.31)	**0.74 (0.63 – 0.87)**
Filipino	308 (72.1)	119 (27.9)	1.33 (1.08 – 1.65)	0.94 (0.74 – 1.19)
South Asian I/P	476 (58.7)	335 (41.3)	**0.73 (0.64 – 0.84)**	1.03 (0.88 – 1.21)
Age				
≤40	2283 (61.0)	1458 (39.0)	1.00 (reference)	1.00 (reference)
41-50	15372 (73.4)	5562 (26.6)	1.76 (1.64 – 1.90)	1.39 (1.28 – 1.51)
51-60	35419 (73.0)	13104 (27.0)	1.73 (1.61 – 1.85)	1.46 (1.35 – 1.58)
61-70	26052 (64.5)	14320 (35.5)	1.16 (1.08 – 1.24)	1.17 (1.08 – 1.27)
70+	14256 (51.0)	13692 (49.0)	0.66 (0.62 – 0.71)	0.82 (0.75 – 0.89)
Site Group				
Oral Cavity	16208 (47.0)	18263 (53.0)	0.12 (0.11 – 0.12)	0.12 (0.11 – 0.12)
Oropharynx	48659 (88.4)	6382 (11.6)	1.00 (reference)	1.00 (reference)
Non-Oropharynx	9491 (84.8)	1700 (15.2)	0.73 (0.69 – 0.78)	0.74 (0.69 – 0.78)
Larynx	19024 (46.6)	21791 (53.4)	0.12 (0.11 – 0.12)	0.12 (0.11 – 0.12)
Insurance				
Private	43105 (67.1)	21112 (32.9)	1.00 (reference)1.38	1.00 (reference)
Other Govt	2529 (73.8)	897 (26.2)	(1.28 – 1.49)	1.64 (1.50 – 1.79)
Medicare	28384 (57.9)	20665 (42.1)	0.67 (0.66 – 0.69)	1.21 (1.17 – 1.25)
Medicaid	9657 (81.1)	2250 (18.9)	2.10 (2.00 – 2.21)	2.75 (2.61 – 2.90)
Uninsured	6361 (76.7)	1935 (23.3)	1.61 (1.53 – 1.70)	2.00 (1.89 – 2.12)
Residence				
Urban	84177 (66.1)	43158 (33.9)	1.00 (reference)	--
Rural	5999 (64.0)	3371 (36.0)	0.91 (0.87 – 0.95)	
Period of diagnosis				
2011 – 13	33993 (68.8)	15427 (31.2)	1.00 (reference)	--
2004 – 10	59389 (64.5)	32709 (35.5)	0.82 (0.80 – 0.84)	
Area-level educational attainment			1.00 (reference)	
<7%	20785 (64.9)	11261 (35.1)	1.04 (1.01 – 1.07)	1.00 (reference)
7-12.9%	31038 (65.7)	16198 (34.3)	1.08 (1.05 – 1.12)	1.14 (1.10 – 1.18)
13-20%	25423 (66.6)	12742 (33.4)	1.09 (1.05 – 1.13)	1.18 (1.14 – 1.22)
>=21%	14659 (66.9)	7264 (33.1)		1.21 (1.16 – 1.26)
Area-level Income				
$63k+	27317 (65.4)	14461 (34.6)	Ref	--
$48k - <$63k	25398 (66.1)	13030 (33.9)	1.03 (1.00 – 1.06)	
$38k - <$48k	23563 (65.8)	12242 (34.2)	1.02 (0.99 – 1.05)	
<$38k	15573 (66.9)	7702 (33.1)	1.07 (1.03 – 1.11)	

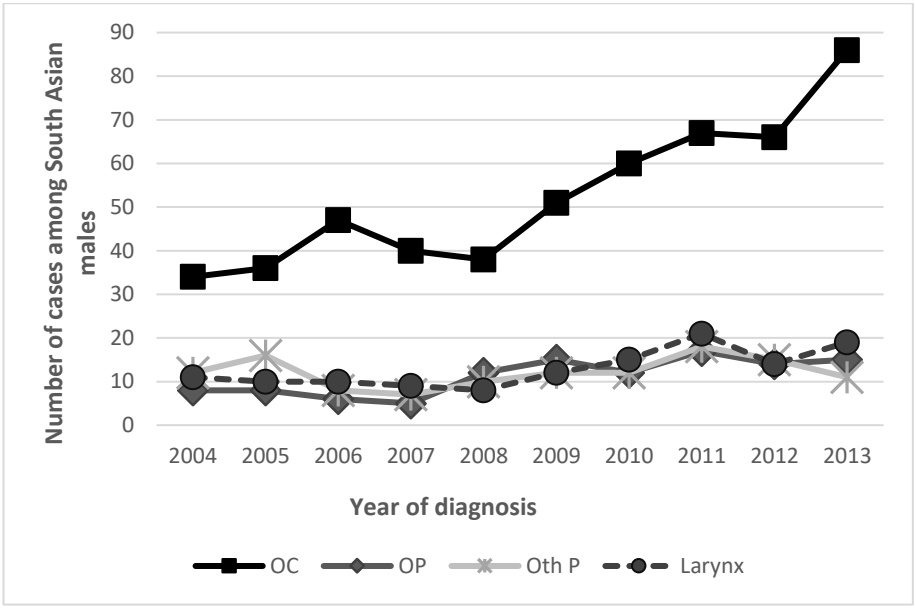
[a] Adjusted for age at diagnosis, site group, insurance and area level education

Figure 10: Temporal trends in HNSCC cases among males in three largest Asian groups in the US.

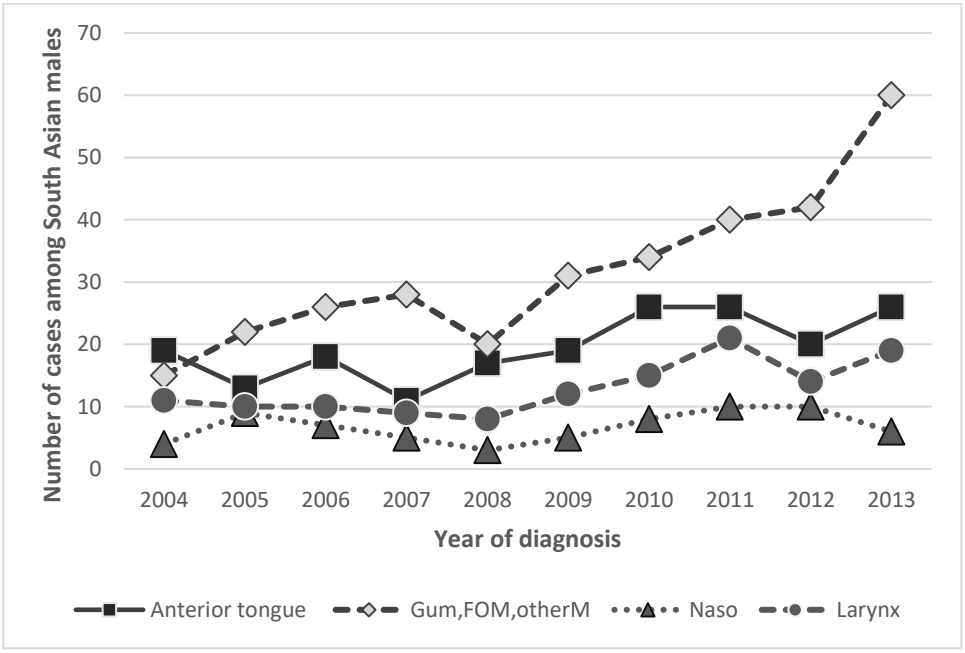


In Chinese males, although Non-OPCs were the predominant type of HNSCCs, there was no appreciable change in the number of cases from 64 cases in 2004 to 66 cases in 2013. There was some increase in OPC cases (from 4 cases in 2004 to 11 cases in 2013) but the numbers are still low to detect any significant trend (APC=6.47; p=0.15) (Figure 12). The predominant type of HNSCC in Filipino males (Figure 13) was Non-OPC, like Chinese, and the zig-zag temporal pattern of Non-OPC cases was more prominent for Filipinos than Chinese males.

Figure 11: Temporal trends by HNSCC site group (a) and the predominant primary HNSCC subsites (b) among South Asian I/P males.

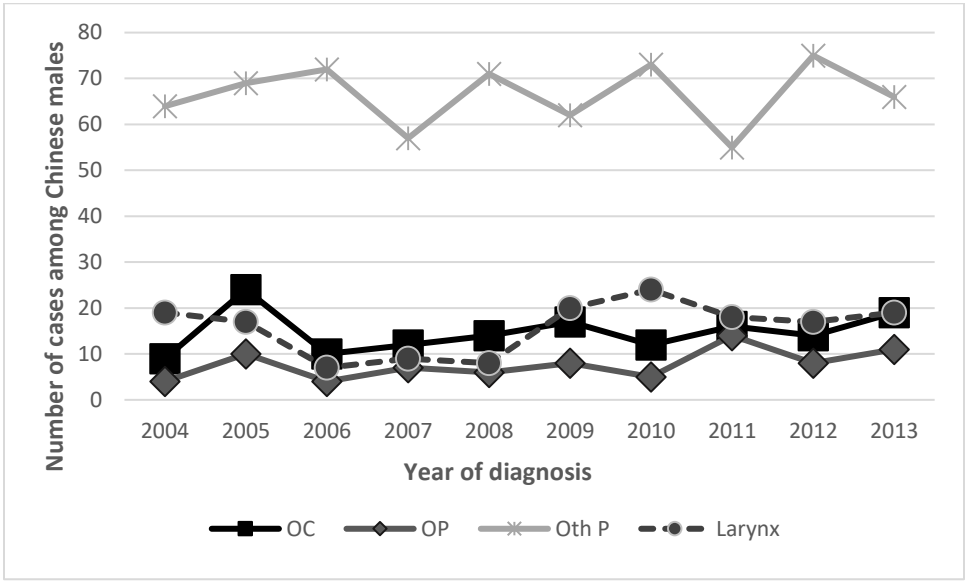


11(a)

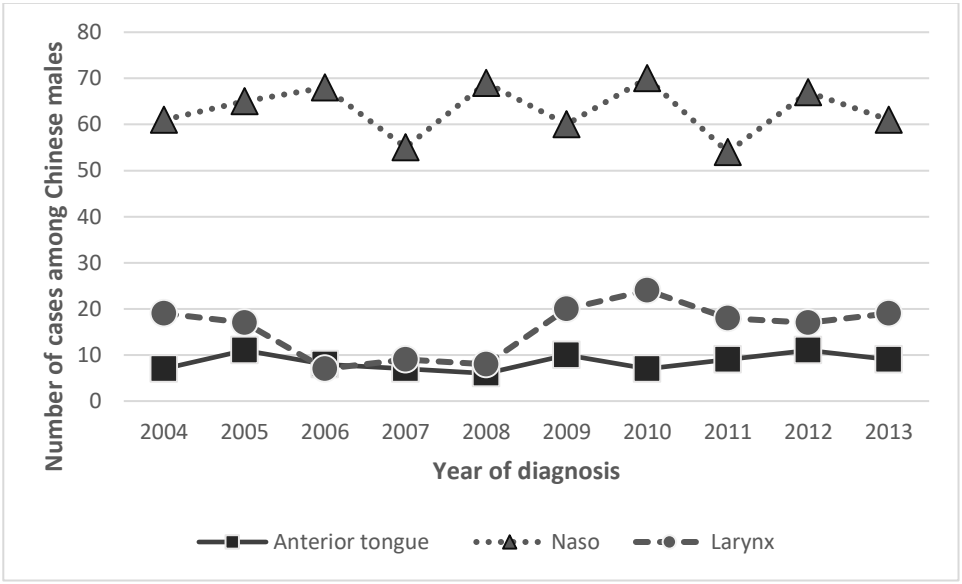


11(b)

Figure 12: Temporal trends by HNSCC site group (a) and the predominant primary HNSCC subsites (b) among Chinese males

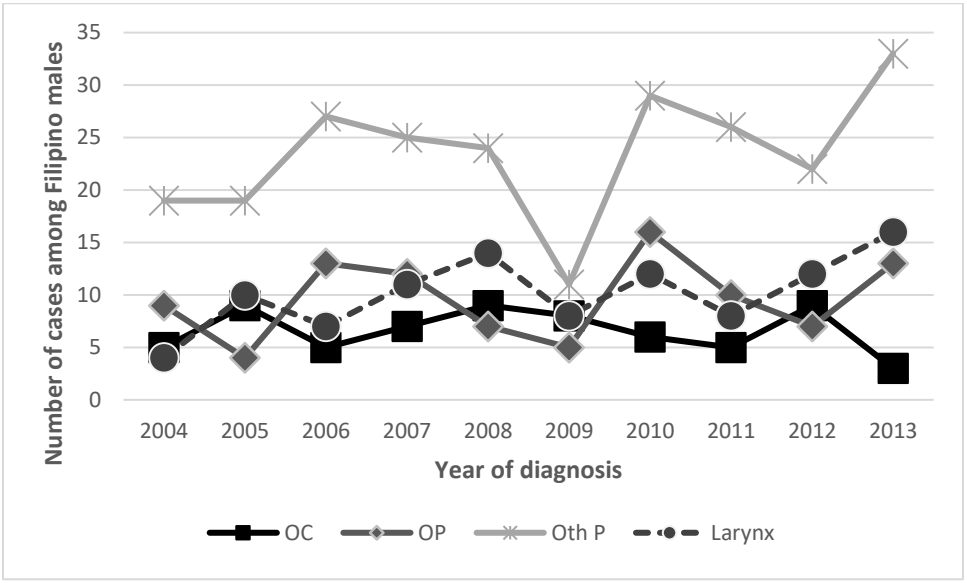


12(a)

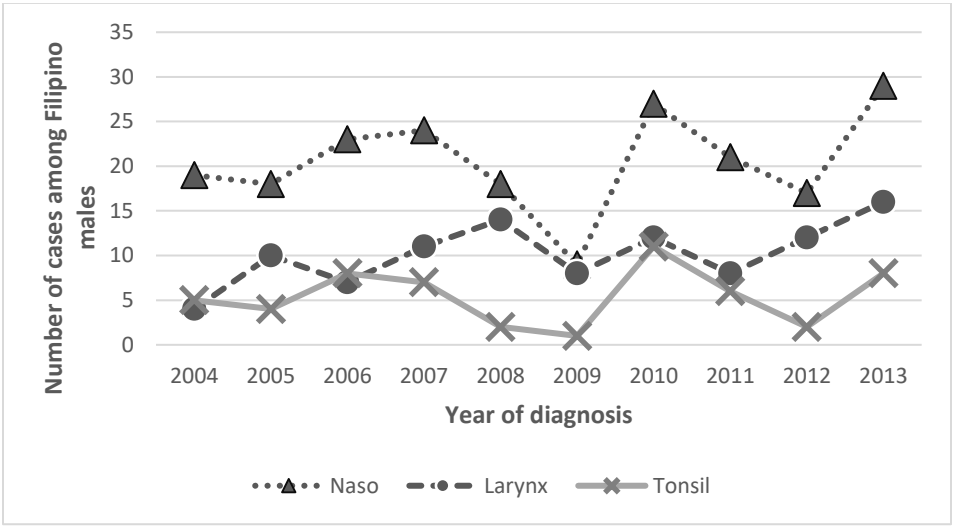


12(b)

Figure 13: Temporal trends by HNSCC site group (a) and the predominant primary HNSCC subsites (b) among Filipino males



13(a)



13(b)

D. **Discussion**

In the past few years, OPCs have garnered a lot of attention in the US, largely due to the increase in HPV positive OPC cases among White males (Chaturvedi et al., 2011; Simard et al., 2014). However, the sites that we hear less about in the US pose a much higher risk in certain ethnic subpopulations. In our study, South Asian I/P males had seven times higher odds of having OCC, Chinese had 34 times higher odds of having Non-OPC and Filipinos had more than 10 times higher odds of having Non-OPC (relative to OPC), when compared to NHW males, even after adjusting for covariates. These findings reveal the importance of other head and neck sites in specific racial/ethnic populations that comprise a small growing part of the total US population but, nonetheless, comprise a high-risk population.

Chinese, South Asian I/P and Filipinos comprised 56% of the total HNSCC cases in Asian males in the US from 2004 to 2013. While there was an overall increase in the number of HNSCC cases in all these three groups, South Asian I/P males had the largest increase. For this group, the number of overall HNSCC cases increased by 101% and OCC, specifically, increased by 153% from 2004 – 2013. This percentage increase in OCC was greater than the population increase of this diaspora. Of all the subsites within oral cavity, it was gum, floor of mouth and buccal mucosa (combined) that was largely responsible for this increase, as the number of South Asian males diagnosed with cancers of these subsites increased by 300% from 15 cases in 2004 to 60 cases in 2013. These specific subsites include the bucco-gingival sulcus, which is the predominant site for OCC in India accounting for two-thirds of the total OCC cases. This is the site where betel quid or *paan* (areca nut, mixed with slaked lime, flavoring and sometimes tobacco wrapped inside a betel leaf) and smokeless tobacco is kept in the mouth for long periods of time (Kulkarni, 2013, Warnakulasuriya, 2009). It is known that the incidence of OCC in

Indian subcontinent (IARC GLOBOCAN 2018, 2019; Warnakulasuriya, 2009) and nasopharyngeal cancer in China is high (Cao et al., 2011; Jia et al., 2006). Consistent with these patterns, we found that the predominant site group for HNSCCs in South Asian I/P was oral cavity and in Chinese males it was non-oropharynx (specifically nasopharynx). Like Chinese, the predominant site group for Filipinos was also nasopharynx, possibly because Filipinos include persons of Chinese heritage, given that more than 23% of the population in Philippines is of Chinese descent (Senate of the Philippines, 18th Congress, 2013). These findings indicate that the predisposition for particular sites in head and neck region continues in these diasporas despite migration, suggesting a continuation of high-risk behaviors post migration to the US, given that a high proportion of Asians (69% Asian Indian, 67% Pakistani, 63% Chinese and 52% Filipinos) in the US are foreign born and a large chunk of these have lived here longer than 10 years (Pew Research Center, 2019). Genetic susceptibility combined with early life exposures, such as salt-cured and nitrosamine-rich food, may also play a role, especially for nasopharyngeal cancers (Shield et al., 2017). In sharp contrast to the sites observed among Asians subgroups, OPCs were more common in NHW males. Although, overall Filipinos had a larger proportion of late stage diagnoses, the difference was not statistically significant. Only Chinese had a significantly lower odds of late stage diagnosis in comparison to NHW.

Our findings are consistent with the studies conducted on Asians diasporas in other countries. In a study conducted in South East England, the risk of OCC was higher in South Asians in comparison to Non-South Asian males (Moles et al., 2008). Another study done in Southern England found the risk of nasopharyngeal cancer to be higher in Chinese and risk of oral cancer to be high in (South) Asians (Warnakulasuriya et al., 1999). However, few studies that have ventured into head and neck cancers among Asians in the US, have overlooked

differences by sites within head and neck region. Jin et al 2016 studied incidence of 17 major cancers in Asians and found the incidence of cancer of oral cavity and pharynx, combined, to be lower in all seven major Asian subpopulations (including South Asian, Chinese and Filipinos) than NHW (Jin et al., 2016). However, combining these two sites together is potentially misleading, since different sites carry different risks among these populations owing to differences in risk factors. This may also explain why Rastogi et al (2007) found the incidence of cancer of oral cavity and pharynx, combined, to be lower in South Asian diaspora than Whites using data from 1999-2001 (Rastogi et al., 2007).

Diagnosis at a younger age was much more common in Asian subpopulations. These findings are consistent with those reported in England (Warnakulasuriya et al., 1999). In our study, Chinese males were five times more likely to be diagnosed by age 40, while South Asian I/P and Filipino males had four and three times, respectively, higher likelihood of being diagnosed by age 40, when compared to NHW males. Similarly, diagnosis by age 30 was also more common in Asian groups, with Chinese having six times higher likelihood than NHW. This is a key finding as diagnosis at an early age means these cases live longer with the impact of cancer and treatment related complications, disfigurement, including facial changes, functional changes to speech and swallowing, disability and diminished quality of life. These younger Chinese and South Asian I/P males were less likely to be HPV positive than NHW. Moreover, previous research has shown Asians to be less likely to use tobacco and alcohol than other racial/ethnic groups (Adams et al., 2016; Martell et al., 2016). Among Asians, Chinese and Asian Indians have the lowest rates of smoking (Martell et al., 2016) but the role of smokeless tobacco cannot be ruled out, especially for South Asians who have been reported to have higher prevalence of smokeless tobacco (Glenn, Surani, Chawla, & Bastani, 2009) and areca nut use.

Besides this, the efforts of tobacco industry in promoting tobacco use in Asian American communities (Asian Pacific Partners for Empowerment, Advocacy & Leadership, n.d.; CDC, 2019) and the early initiation of smoking in young adulthood in Asians (Asian Pacific Partners for Empowerment, Advocacy & Leadership, n.d.; Trinidad et al., 2004) may have also potentially contributed. Moreover, areca nut, which is a major risk factor for OCCs in South Asia, is widely available in most South Asian grocery stores in the US and through online shopping; thus, making it easy for migrants to continue the habit and potentially pass it on to the younger generation. In fact, initiation of areca nut chewing habit has been reported in adolescents as young as 13 – 15 years of age in India (Gunaseelan et al., 2007). Since the use of areca nut and tobacco is addictive, there is an urgent need to discourage the initiation and continuation of these habits in Asian American youth by increasing awareness and restricting access through policy changes.

Although overall a large proportion of the OPC cases had unknown HPV status, among those with known status, HPV 16/18 was less common in South Asian I/P and Filipino subgroups, compared to NHW. The high proportion of cases with unknown status is understandable considering that HPV testing recommendations came into effect only recently for OPCs (College of American Pathologists, 2017).

Hot tea which is widely consumed in South Asia and China is another factor worth considering. Consumption of hot tea has been found to be associated with esophageal cancer (Islami et al., 2020; Lin et al., 2020). Even though a similar association has not yet been reported for HNSCCs, it cannot be completely ruled out considering that drinking of another hot beverage, maté (traditionally drunk as a very hot beverage in parts of South America), has been shown to be associated with OCC and OPC (summary OR=2.1; 95% CI: 1.4 – 3.2 (Dasanayake

et al., 2010)) in studies from Brazil (Pintos et al., 1994) and Uruguay (De Stefani et al., 1987). Chronic thermal injury from hot beverages and potential chemical carcinogenesis (Dasanayake et al., 2010; Goldenberg et al., 2003; Islami et al., 2020; Lin et al., 2020) is likely to play a role. Nonetheless, some studies have also reported a protective effect of tea (Huang et al., 2014; Zhang et al., 2014) (and coffee (Galeone et al., 2010; Miranda et al., 2017)) consumption against HNSCCs.

With such high predisposition for HNSCC of certain sites, it is important to consider screening in these subgroups. Early detection will not only save lives but can also limit the functional and physical impact of the cancer and its treatment. As compared to other head and neck cancers, OCC is easy to screen. The screening is non-invasive and fast and can be done by visual and tactile examination. Currently, US Preventive Services Task Force does not recommend routine oral cancer screening in asymptomatic individuals (US Preventive Services Task Force, 2013) but states and regions with higher Asian populations should work towards promoting screening among these subpopulations. Considering the higher odds of OCC observed in our study in South Asian I/P males, clinicians and dental practitioners should be vigilant when they come across patients from high risk groups. Clinicians, especially, can play a key role because migrants from minority groups may not have dental insurance or access to a dentist, therefore, primary care provider may be their only point of access to care. Similarly, clinicians should also be cognizant of the higher risk of non-OPCs among not just Chinese but also Filipino males. Cultural awareness regarding use of risk factors specific to these diasporas may help physicians/dentists in asking appropriate questions, increasing awareness and encouraging discontinuation of risky behaviors.

Our study had several limitations. Given that the outcome is not rare, the magnitude of ORs in our study is likely to be exaggerated. Even then, we cannot deny that the likelihood of cancers of certain sites was much higher in these Asian groups compared to NHW. Another limitation is that HPV status could not be studied further because of extremely low numbers of HPV positive OPC cases among Asians. We also did not have information whether the cases in our study were foreign born or US born. However, from what we know based on the population growth and the US Census, it can be assumed that a high percentage of these are likely to be foreign born. One more limitation is that we did not have risk factor (such as smoking, EBV, diet) information; therefore, we could not assess the differences in distribution of risk factors. Moreover, individual level socio economic indicators were not available. We did, however, have zip-code level socio-economic information, which may serve as a proxy for individual level SES.

Our study had some strengths. This is the first study to examine HNSCC sites and stage at diagnosis in-depth among three largest Asian diasporas in the US. Prior literature has either reported rates for Asian Americans as a group without accounting for variations within this heterogeneous group or have examined oral cavity and pharynx as a single site, without exploring specific head and neck sites, besides nasopharynx (Jin et al., 2016). The study had a large sample, even for Asian subgroups, from all regions of the US, thereby allowing us to comprehensively study the characteristics of HNSCC cases along with temporal trends in these Asian diasporas.

E. **Conclusion**

Although OPCs have been getting attention lately in the Western world, including the US, due to rise in HPV-associated cases, other HNSCCs have been silently on a rise, albeit on a

smaller scale, in specific Asian diasporas. Even though overall Asians may be doing better in health parameters, Asian diasporas are at a higher likelihood of specific HNSCCs, possibly due to certain risk factors. As Asians comprise the fastest growing population in the US, the cases of HNSCCs, including OCC and Non-OPC, are likely to continue to rise, owing to migration and continuation of high-risk behaviors. Risk factors, screening and survival need to be studied further in these subpopulations. Primary prevention, in the form of targeted risk factor reduction strategies, and secondary prevention, through screenings, should be considered for specific high-risk populations. Future studies should also explore HNSCCs among women of Asian diaspora.

VI. SURVIVAL IN HEAD AND NECK SQUAMOUS CELL CARCINOMA CASES AMONG MALES OF THREE LARGEST ASIAN DIASPORAS IN THE US, 2004 -2012

A. Introduction

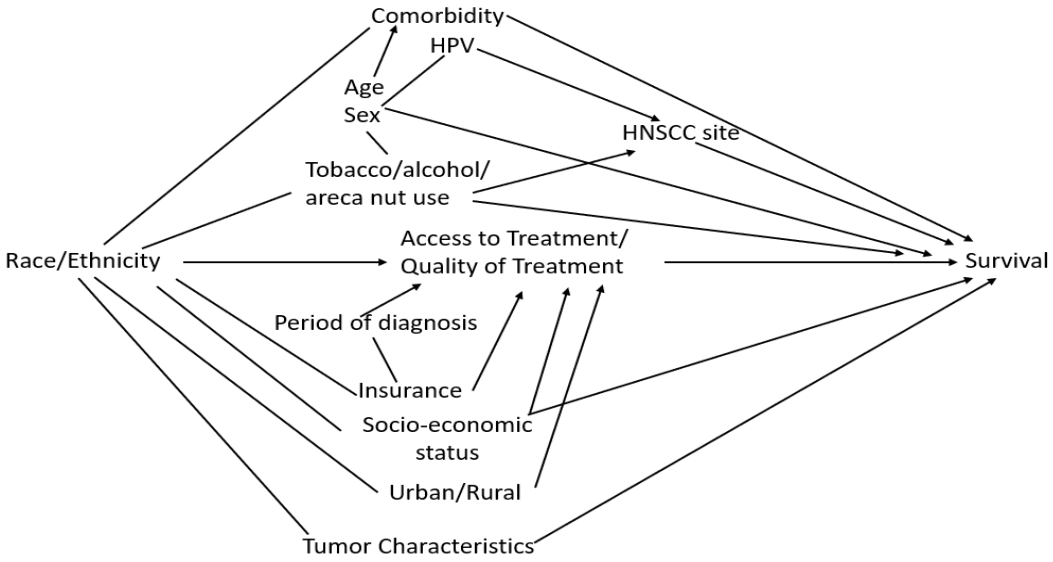
Asians are the fastest growing minority group in the US. Chinese, South Asian I/P and Filipinos are the three largest Asian groups in the US, accounting for more than three-fifths of the Asian population in the US (Pew Research Center, 2019). Given their higher likelihood for HNSCCs of certain sites (as established in Aim 2) consistent with the patterns observed in their native countries that also have high rate of mortality associated with these specific sites (such as, OCC mortality in South Asia is double that of global rate (Ahluwalia, 2005; Ferlay et al., 2015), nasopharyngeal cancer mortality is high in South China (Wei et al., 2014)), it is important to study differences in survival in these groups in the US.

Both site of cancer (Carvalho, André Lopes, Nishimoto, Califano, & Kowalski, 2005; Pulte & Brenner, 2010) and HPV status are important prognostic factors as HPV related cancers tend to have better survival (Chaturvedi et al., 2008; Gillison et al., 2000) than HPV unrelated cancers with 82% of HPV positive OPC patients surviving for three years compared to 57 percent in smoking related (HPV negative) OPCs, after adjusting for age, race and stage (Ang et al., 2010). Moreover, HPV positive HNSCCs are also more sensitive to chemotherapy and radiotherapy (Cleveland et al., 2011); thereby leading to better survival. As established in Aim 2, the Asian subgroups are less likely to be HPV 16/18 positive when compared to NHW males. Literature on survival in these Asian subgroups, or Asians, in general, is extremely limited. An abstract published in 2018 found the overall survival to be better in nasopharyngeal cancer cases of Asian race compared to Whites (Anderson E., Yoshida E.J., Mita A., Scher K., Shiao S.L.,

Mallen-St.Clair J., Ho A.S., Zumsteg Z.S., 2018). Studies from other developed countries also show that Asians have better survival. An abstract published in 2014 compared Asians to non-Asians in Canada and found Asians to be more likely to have OCC, worse prognostic features and large tumors but better survival than non-Asians (Kim et al., 2014).

The purpose of the study was to examine the all-cause mortality and overall survival in male HNSCC cases among three of the largest Asian subgroups in the US and compare them to NHW. After having established the differences in site group and HPV status (for OPCs) in these groups, it is important to study whether these differences translate into differences in survival. We also examined factors associated with any observed survival difference between these groups. The conceptual framework for the association of race/ethnicity with survival presented in Figure 14 was used to guide the analysis of this study. Race/ethnicity is likely a predictor of survival as it affects a person's access to treatment. There may also be a genetic component (not shown in figure) where certain racial/ethnic groups are predisposed to more aggressive tumors that lead to lower survival (Özdemir & Dotto, 2017). Insurance, rural residence and SES are other variables that are predictors of access to treatment; therefore, they are indirect predictors of survival. Access to treatment is a mediator here. Tobacco/alcohol and HPV are predictors of the site where tumor develops, and different HNSCC sites have different survival rates. However, tobacco/alcohol and HPV (for OPCs) can also directly affect survival because studies in the past have shown that tobacco use is linked to poorer prognosis and HPV is linked to better prognosis (Chaturvedi et al., 2008; Gillison et al., 2000; Gillison et al., 2012). We did not have tobacco/alcohol information so we could not control for it. Therefore, insurance, rural residence and SES were potential confounders. Other potential confounders were clinical and histologic

Figure 14: Conceptual framework for the association of race/ethnicity with survival in HNSCC cases.



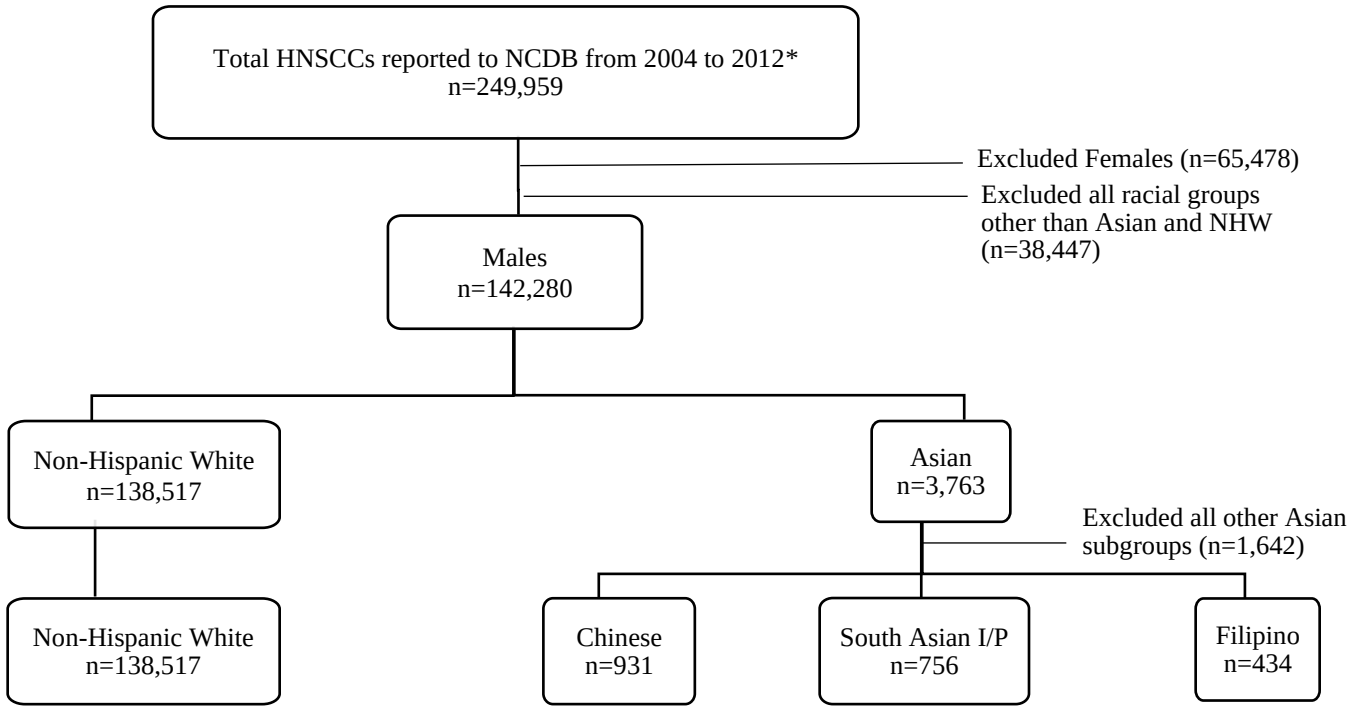
characteristics of tumor (such as, grade, stage and spread). Stage at diagnosis was also examined as a potential effect modifier of the relationship between race/ethnicity and survival.

B. **Methods**

1. **Study Population**

Secondary data from National Cancer Database (NCDB) for 2004 -2012 (Figure 15) were used for studying overall survival among male HNSCC cases from three largest Asian subpopulations in the US, including Chinese, South Asian I/P, and Filipinos (US Census Bureau, 2017), and compare them to NHW. Unlike aim 1 and 2, cases diagnosed in 2013 were not included in aim 3 because vital status was not available in our dataset for those who were diagnosed in 2013.

Figure 15: Flowchart of the study population and the sample size.



* Vital status was not available for cases reported in 2013; therefore, the analysis was limited to 2004 to 2012

2. **Variables**

a. **Outcome Variable**

All-cause mortality was the main outcome variable. Time from diagnosis to death or last follow-up was used for survival analysis. Survival in years was calculated by dividing the time elapsed (in months) between the date of diagnosis and the date of last contact or date of death by 12.

b. **Exposure Variable and the Covariates**

Grade of the tumor was classified as well differentiated, moderately differentiated, poorly differentiated, undifferentiated (anaplastic) and undetermined (Peterson et al., 2016), where well differentiated is the referent because it has the closest resemblance to normal tissue. Behavior of the tumor was categorized as carcinoma-in-situ and invasive. Analytic tumor stage at diagnosis was categorized as 0, I, II, III, IV, unknown/not applicable. Tumor stage was also categorized as late stage (Stage III-IV) and early stage (Stage I-II) for a part of the analysis. Spread of the tumor was categorized as local, local-regional and distant (Peterson et al., 2016). Treatment, a covariate in the analysis, was categorized as surgery (± chemotherapy), surgery + radiotherapy, surgery + chemo-radiotherapy, radiotherapy alone, and chemo-radiotherapy (Cadoni et al., 2017; Chen et al., 2009) for the main analysis (finer categorization was used for presenting a detailed treatment table). Most of the prior studies that have examined survival in HNSCC cases, have used similar categories for treatment or have reduced it to fewer categories (Cadoni et al., 2017; Chen et al., 2009; Leoncini et al., 2015; Murphy et al., 2016). Time to treatment initiation was classified as ≤30, 31-60, 61-90 and 91-365 days. We used 365 days as cut-off because of concerns with miscoding (Murphy et al., 2016).

3. **Statistical Analyses**

After univariate analysis was done to examine the distribution of variables, bivariate analyses were conducted to examine the association of vital status with race/ethnicity and other demographic and clinical variables. As race/ethnicity was the main exposure of interest, bivariate analysis was also done to examine the association of race/ethnicity with covariates identified through conceptual model. For normally distributed continuous variables (age at diagnosis and

years of survival), one-way ANOVA was used to assess the difference in means among racial/ethnic groups. For non-normally distributed continuous variables (distance between patient residence and the reporting hospital, and the time to treatment initiation in days), Kruskal-Wallis test was used to assess difference in mean. Correlation between tumor characteristics was assessed by calculating correlation coefficients as presented in Table XI. Stage and Spread were highly correlated but for the other variables, the correlation was low.

TABLE XI

CORRELATION AMONG TUMOR CHARACTERISTICS IN HNSCC CASES

	Stage	**Behavior**	**Grade**	**Spread**
Stage	1.00	0.33 p<.0001	-0.01 p=0.0027	**0.84** **p<.0001**
Behavior	0.33 p<.0001	1.00	-0.28 p<.0001	0.06 p<.0001
Grade	-0.01 p=0.0027	-0.28 p<.0001	1.00	0.09 p<.0001
Spread	**0.84** **p<.0001**	0.06 p<.0001	0.09 p<.0001	1.00

Log rank test was used to compare the survival by race/ethnicity using the Kaplan-Meier product-limit approach. Before assessing the association of race/ethnicity with overall survival, Proportional Hazards assumption was examined for the exposure variable (race/ethnicity) and all the covariates (i.e., age at diagnosis, geographic area of the facility, tumor site group, insurance status, type of facility, area level income quartiles, area level education quartiles, behavior,

grade, spread, treatment, distance from the facility, time to treatment initiation, stage, period of diagnosis and Charlson/Deyo comorbidity score) identified from the conceptual model, both visually, by using survival function vs. time and log (-log(survival)) vs. log(time) graphs, and statistically, by using interaction with time and natural log of time in the model. The assumption was accepted as met if the survival curves were parallel (for most part) and/or the interaction term was non-significant. For the main exposure, race/ethnicity, although the survival curves for the three Asian groups (Chinese, South Asian I/P, and Filipino) were not entirely parallel to each other, they were; however, parallel to NHW (the referent group) for the most part. Moreover, the interaction terms with time (p=0.41) and with natural log of time (p=0.74) were both non-significant. Therefore, the proportional hazards assumption was met for the race/ethnicity variable. The assumption was however, not met for most of the covariates. Hence, these covariates were used as stratification variables in the final Cox regression model.

Cox Proportional Hazards models were run to assess the association of race/ethnicity with mortality. The initial multivariate model included all the covariates identified in the conceptual model. Tumor stage and site group were identified *a priori* as potential effect modifiers; therefore, these two were considered for inclusion as interaction terms (i.e., interaction of site group with race/ethnicity, and interaction of stage with race/ethnicity) in the multivariate model to assess effect modification. A p-value of 0.05 was decided as the cut-off for inclusion of interaction term in the model. As both the interactions were non-significant, they were dropped out of the model. Manual backward elimination procedure was used where each covariate was dropped out of the model one at a time and the effect on measure of association of the main exposure variable (race/ethnicity) was noticed. If the Hazard Ratios for any of the exposure levels (Chinese vs. NHW, South Asian I/P vs. NHW, and Filipino vs. NHW) changed

by ≥10% when a covariate was dropped, then the covariate was considered a confounder and was brought back in the model. If a variable was not a confounder, it was dropped from the model. However, certain variables were retained in the final model because they are strong conceptual confounders even though they were not confounding the association of race/ethnicity with mortality in this analysis. All the covariates that met the proportional hazards assumption were included in the MODEL statement along with the main exposure, and the covariates that did not meet the assumption (but were identified as potential confounders in conceptual model) were included in STRATA statement. Kaplan Meier survival curves and log rank test were used to examine survival difference by race. Adjusted survival curves were also created to look for survival differences after adjusting for covariates.

To obtain Hazard Ratios for the association of race/ethnicity with mortality within each tumor site group, tumor stage, area level median income quartile and education quartile, the final model was re-run in each of the subgroups. Kaplan Meier curves were also obtained for each of the subgroups.

C. **Results**

Of our total analytic sample of 140,638 cases, 931 Chinese (0.7%), 756 South Asian I/P (0.5%), 434 Filipino (0.3%) and 138517 NHW males (98%) were diagnosed with HNSCCs between 2004-2012. As established in Aim 2, Asian subgroups had higher likelihood of being diagnosed at a younger age (diagnosis by age 40 was six-fold higher among Chinese than NHW males), having private insurance, residing in zip codes with higher median household income and had lower estimated travel distance to the reporting facility. Table XII summarizes the clinical characteristics by race/ethnicity. Apart from the differences in distribution of site groups

TABLE XII

CLINICAL CHARACTERISTICS AMONG HNSCC CASES IN MALES OF CHINESE, SOUTH ASIAN I/P[a] AND FILIPINO ORIGIN IN THE US IN COMPARISON TO NON-HISPANIC WHITES, 2004 – 2012.

	Chinese males (N=931) n (%)	South Asian[a] males (N=756) n (%)	Filipino males (N=434) n (%)	NHW males (N=138517) n (%)	P value
Age at diagnosis					<0.0001
Mean [SD]	56.6 [14.5]	57.6 [13]	59.7 [13]	60.9 [11]	
Median	56	58	59	60	
Age categories					<0.0001
≤40	**133 (14.3)**	**80 (10.6)**	**38 (8.8)**	**3629 (2.6)**	
41-50	**188 (20.2)**	**145 (19.2)**	**67 (15.4)**	**20688 (14.9)**	
51-60	253 (27.2)	212 (28.0)	126 (29.0)	46923 (33.9)	
61-70	179 (19.2)	179 (23.7)	107 (24.6)	39079 (28.2)	
>70	178 (19.1)	140 (18.5)	96 (22.1)	28198 (20.4)	
Insurance[b]					<0.0001
Private	454 (50.4)	380 (52.3)	228 (54.4)	63360 (47.3)	
Other Govt	6 (0.7)	1 (0.1)	12 (2.9)	3279 (2.4)	
Medicare	210 (23.3)	148 (20.4)	94 (22.4)	48529 (36.2)	
Medicaid	176 (19.5)	106 (14.6)	57 (13.6)	11013 (8.2)	
No Insurance	55 (6.1)	**91 (12.5)**	28 (6.7)	7868 (5.9)	
Period of Diagnosis					0.002
Pre ACA (2004-10)	714 (76.7)	524 (69.3)	335 (77.2)	103468 (74.7)	
Post ACA (2011-12)	217 (23.3)	232 (30.7)	99 (22.8)	35049 (25.3)	
Area Level Median Household income[c]					<0.0001
$63,000+	**443 (48.0)**	**388 (52.9)**	**229 (53.5)**	**40485 (29.8)**	
$48,000-$62,999	201 (21.8)	180 (24.5)	121 (28.3)	37573 (27.6)	
$38,000-$47,999	165 (17.9)	107 (14.6)	50 (11.7)	35101 (25.8)	
<$38,000	114 (12.4)	59 (8.0)	28 (6.5)	22853 (16.8)	
Area Level Educational Attainment (% with No HSD)[d]					<0.0001
<7% HSD	182 (19.7)	221 (30.1)	56 (13.1)	31396 (23.1)	
7-12.9% HSD	232 (25.1)	219 (29.8)	134 (31.3)	46217 (34.0)	
13-20% HSD	181 (19.6)	159 (21.6)	123 (28.7)	37267 (27.4)	
>=21% HSD	**328 (35.5)**	136 (18.5)	115 (26.9)	**21215 (15.6)**	
Rural Residence[e]					<0.0001
Yes	3 (0.3)	7 (1.0)	12 (2.8)	9160 (6.9)	
No	903 (99.7)	714 (99.0)	414 (97.2)	124365 (93.1)	
Type of Facility					<0.0001
Academic/research	404 (49.9)	437 (64.1)	170 (42.6)	56556 (41.7)	
Community cancer	95 (11.7)	48 (7.0)	50 (12.5)	14740 (10.9)	
Comprehensive Com	195 (24.1)	163 (23.9)	164 (41.1)	55984 (41.3)	
Integrated Network	116 (14.3)	34 (5.0)	15 (3.8)	8207 (6.1)	
Geographic Area of Reporting Facility[f]					<0.0001
Midwest	45 (5.6)	137 (20.1)	30 (7.5)	35546 (26.2)	
North East	259 (32.0)	263 (38.6)	52 (13.0)	25775 (19.0)	
South	58 (7.2)	197 (28.9)	37 (9.3)	53947 (39.8)	
West	448 (55.3)	85 (12.5)	281 (70.2)	20244 (14.9)	

TABLE XII (Continued)

CLINICAL CHARACTERISTICS AMONG HNSCC CASES IN MALES OF CHINESE, SOUTH ASIAN I/P[a] AND FILIPINO ORIGIN IN THE US IN COMPARISON TO NON-HISPANIC WHITES, 2004 – 2012.

	Chinese males (N=931) n (%)	South Asian[a] males (N=756) n (%)	Filipino males (N=434) n (%)	NHW males (N=138517) n (%)	P value
Estimated travel distance to reporting facility[g]					<0.0001
<12.5	**766 (83.4)**	451 (62.0)	**329 (77.8)**	68066 (50.8)	
12.5 to <50	132 (14.4)	243 (33.4)	83 (19.6)	47925 (35.8)	
50 to <250	20 (2.2)	34 (4.7)	11 (2.6)	18034 (13.5)	
Site Group[h]					<0.0001
Oral Cavity	128 (13.8)	**439 (58.1)**	63 (14.5)	34175 (24.7)	
Oropharynx	66 (7.1)	97 (12.8)	83 (19.1)	**50863 (36.7)**	
Non-Oropharynx	**598 (64.2)**	110 (14.6)	**202 (46.5)**	12109 (8.7)	
Larynx	139 (14.9)	110 (14.6)	86 (19.8)	**41370 (29.9)**	
Primary anatomical subsite					<0.0001
Lip	1 (0.1)	12 (1.6)	1 (0.2)	4615 (3.3)	
Gum, FOM, otherM	51 (5.5)	**258 (34.1)**	36 (8.3)	16670 (12.0)	
Tongue (Anterior)	76 (8.2)	**169 (22.4)**	26 (6.0)	12890 (9.3)	
Tongue (Base)	18 (1.9)	46 (6.1)	27 (6.2)	**21188 (15.3)**	
Tonsil	37 (4.0)	33 (4.4)	46 (10.6)	**24536 (17.7)**	
Oropharynx	11 (1.2)	18 (2.4)	10 (2.3)	5139 (3.7)	
Nasopharynx	**569 (61.1)**	61 (8.1)	**176 (40.6)**	3778 (2.7)	
Hypopharynx	27 (2.9)	45 (6.0)	21 (4.8)	6691 (4.8)	
Other Pharynx	2 (0.2)	4 (0.5)	5 (1.2)	1640 (1.2)	
Larynx	139 (14.9)	110 (14.6)	86 (19.8)	**41370 (29.9)**	
AJCC Stage of Diagnosis[i]					<0.0001
0	14 (1.5)	10 (1.3)	6 (1.4)	4274 (3.1)	
I	150 (16.1)	171 (22.6)	58 (13.4)	26749 (19.3)	
II	88 (9.4)	106 (14.0)	47 (10.8)	15511 (11.2)	
III	213 (22.9)	108 (14.3)	71 (16.4)	21997 (15.9)	
IV	326 (35.0)	304 (40.2)	191 (44.0)	58354 (42.1)	
NA/Unk	140 (15.0)	57 (7.5)	61 (14.0)	11632 (8.4)	
HPV status[j] for OPCs only					0.06
HPV 16/18 negative	10 (15.2%)	9 (9.3%)	9 (10.8%)	5436 (10.7%)	
HPV 16/18 positive	7 (10.6%)	3 (3.1%)	1 (1.2%)	4360 (8.6%)	
HPV unknown	49 (74.2%)	85 (87.6%)	73 (88.0%)	41067 (80.7%)	
Tumor Behavior					<0.0001
In situ	14 (1.5)	11 (1.5)	6 (1.4)	4547 (3.3)	
Invasive	917 (98.5)	745 (98.5)	428 (98.6)	133970 (96.7)	
Tumor Grade					<0.0001
Well diff	43 (4.6)	141 (18.6)	28 (6.4)	15364 (11.1)	
Moderately diff	146 (15.7)	297 (39.3)	94 (21.7)	52688 (38.0)	
Poorly diff	220 (23.6)	129 (17.1)	131 (30.2)	34094 (24.6)	
Undiff	254 (27.3)	26 (3.4)	72 (16.6)	1728 (1.2)	
Undetermined	268 (28.8)	163 (21.6)	109 (25.1)	34643 (25.0)	
Tumor Spread					<0.0001
Local	217 (29.6)	251 (42.5)	89 (25.7)	38313 (35.0)	
Localregional	484 (65.9)	312 (52.9)	236 (68.2)	67935 (62.1)	
Distant	33 (4.5)	27 (4.6)	21 (6.1)	3141 (2.9)	

TABLE XII (Continued)

CLINICAL CHARACTERISTICS AMONG HNSCC CASES IN MALES OF CHINESE, SOUTH ASIAN I/P[a] AND FILIPINO ORIGIN IN THE US IN COMPARISON TO NON-HISPANIC WHITES, 2004 – 2012.

	Chinese males (N=931) n (%)	South Asian[a] males (N=756) n (%)	Filipino males (N=434) n (%)	NHW males (N=138517) n (%)	P value
Treatment					<0.0001
Surgery +/- Chemo	98 (11.6)	234 (33.8)	45 (11.2)	30202 (24.1)	
Surgery + Rad	64 (7.6)	110 (15.9)	42 (10.5)	15990 (12.8)	
Surgery + Chemo + Rad	55 (6.5)	106 (15.3)	50 (12.5)	17530 (14.0)	
Radiotherapy	116 (13.8)	70 (10.1)	58 (14.5)	18441 (14.7)	
Chemo + Rad	510 (60.5)	172 (24.9)	206 (51.4)	43282 (34.5)	
Time to treatment initiation					<0.0001
≤30 days	366 (47.1)	355 (51.8)	214 (56.9)	72900 (58.5)	
31-60 days	297 (38.2)	252 (36.8)	114 (30.3)	38766 (31.1)	
61-90 days	87 (11.2)	57 (8.3)	29 (7.7)	9078 (7.3)	
91-365 days	27 (3.5)	21 (3.1)	19 (5.1)	3967 (3.2)	
Charlson/Deyo Index					<0.0001
0	**828 (88.9)**	594 (78.6)	352 (81.1)	111599 (80.6)	
1	95 (10.2)	134 (17.7)	67 (15.4)	20902 (15.1)	
≥2	8 (0.9)	28 (3.7)	15 (3.5)	6016 (4.3)	
Overall Survival in years[k]					<0.0001
Mean [SD]	3.7 [2.6]	3.1 [2.4]	3.8 [2.7]	3.5 [2.6]	
Median	3.3	2.5	3.4	2.9	
Vital Statistics					<0.0001
Dead	271 (29.1)	244 (32.3)	137 (31.6)	54318 (39.2)	
Alive	660 (70.9)	512 (67.7)	297 (68.4)	84199 (60.8)	

[a] South Asian I/P refers to Asian Indian and Pakistani.

[b] Represents primary payer at diagnosis.

[c] Based on 2012 American Community Survey (2008-2012, adjusted for 2012 inflation) median household income in patient's zip code area.

[d] Based on 2012 American Community Survey (2008-2012) percentage of adults without high school diploma in patient's zip code area.

[e] Rurality and urban influence is based on adjacency to metro area estimated by matching the patients' state and county FIPS code (recorded at the time of diagnosis) against 2003 USDA Economic Research Service. Rural areas include those that were completely rural counties non-adjacent to a metro area or urban population (of any size) non-adjacent to a metro area. Urban includes counties in metro areas (of any population size) or urban population (of any size)/completely rural population adjacent to a metro area (USDA Economic Research Service, 2004).

[f] Midwest represents Ohio, Michigan, Indiana, Wisconsin, Illinois, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska and Kansas. North East represents Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey and Pennsylvania. South includes Delaware, District of Columbia, Maryland, Virginia, West Virginia, Kentucky, North Carolina, South Carolina, Tennessee, Georgia, Florida, Alabama, Mississippi, Arkansas, Louisiana, Texas and Oklahoma. West includes Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, California, Oregon, Washington, Alaska and Hawaii (US Census Bureau, n.d.).

[g] Represents the distance between the centroids of the reporting hospital's zip code and patient's residential zip code.

[h] Oral Cavity includes lips, anterior tongue, gums, buccal mucosa, hard palate, and other mouth; Oropharynx includes base of tongue, tonsils besides oropharynx; Non-oropharynx includes nasopharynx, hypopharynx and other pharynx.

[i] AJCC stage at diagnosis represents American Joint Committee on Cancer (edition 6th and 7th) stage at diagnosis.

[j] HPV 16/18 positive represents cases that were positive for HPV 16 or HPV 18 or both, HPV 16/18 negative represents cases that were negative for both HPV 16 and 18 but could be positive for HPV types other than 16/18 (includes "HPV negative for high-risk and low-risk types, HPV negative for high-risk types with no mention of low-risk types, Negative NOS", "HPV positive for low-risk types only", "HPV positive for specified high risk type(s) other than types 16 or 18", "HPV positive for high-risk type(s), NOS, high-risk type(s) not stated", HPV positive NOS risk and type(s) not stated") and HPV unknown includes "Not applicable: Information not collected for this case", "Test ordered, results not in chart", "Test not done (test was not ordered and was not performed), including no pathologic specimen available for HPV testing", "Unknown or no information" ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

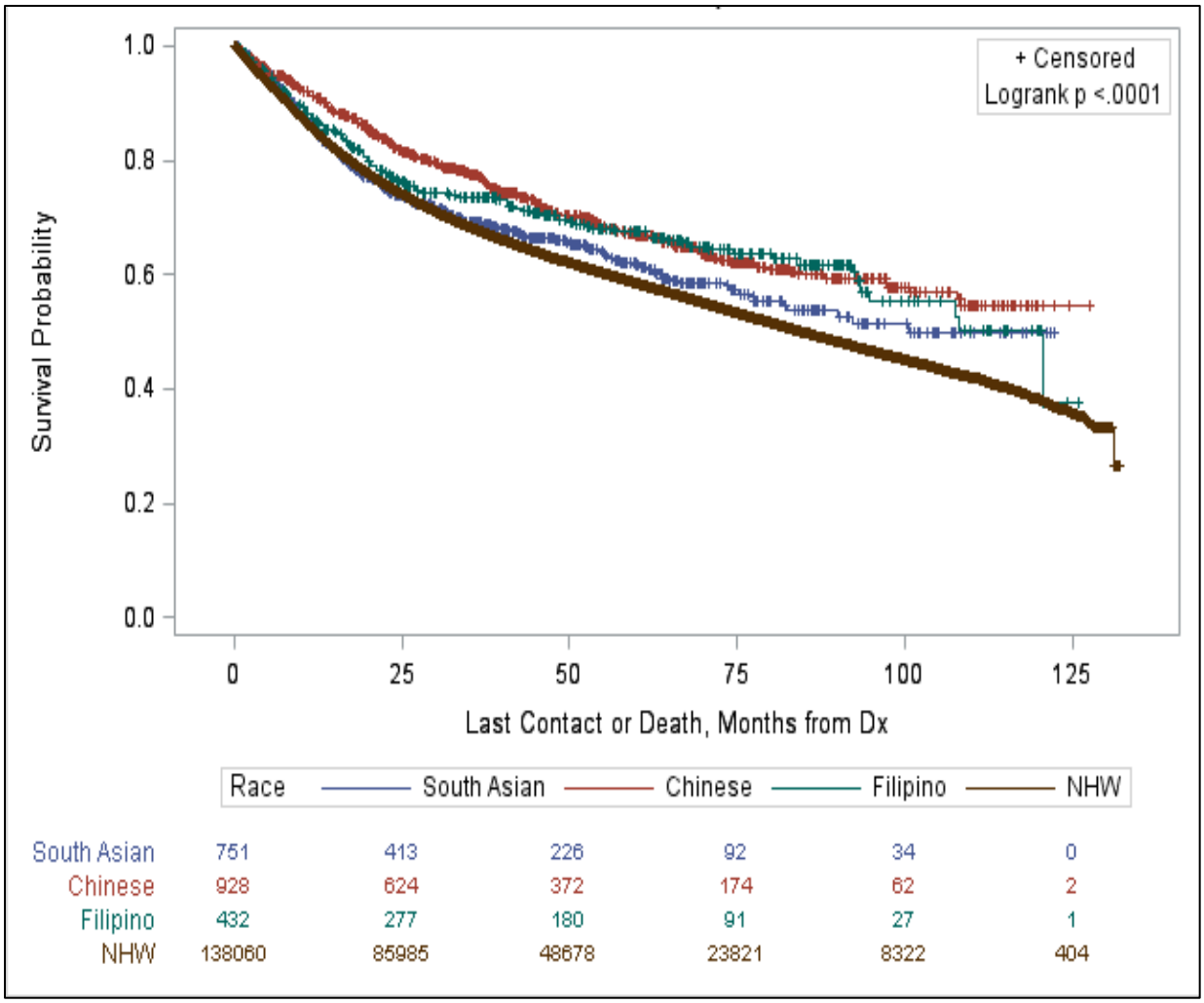
[k] Overall survival in years only accounts for survival over the limited follow up period.

(i.e., OCC in South Asians, Non-OPC in Chinese and Filipinos as opposed to OPC in NHW) and HPV 16/18 status, as observed in Aim 2, interestingly, undifferentiated HNSCCs were much more common in Chinese (27%) and Filipino (17%) males compared to NHW (1%), while localized tumors were more likely in South Asian cases. Surgery (with or without chemotherapy and/or radiation) was much more common in South Asian cases (55%) than other Asian groups (26% in Chinese and 34% in Filipino) but was comparable to NHW (51%). Chinese cases were less likely to report comorbidities, therefore, suggesting better overall health.

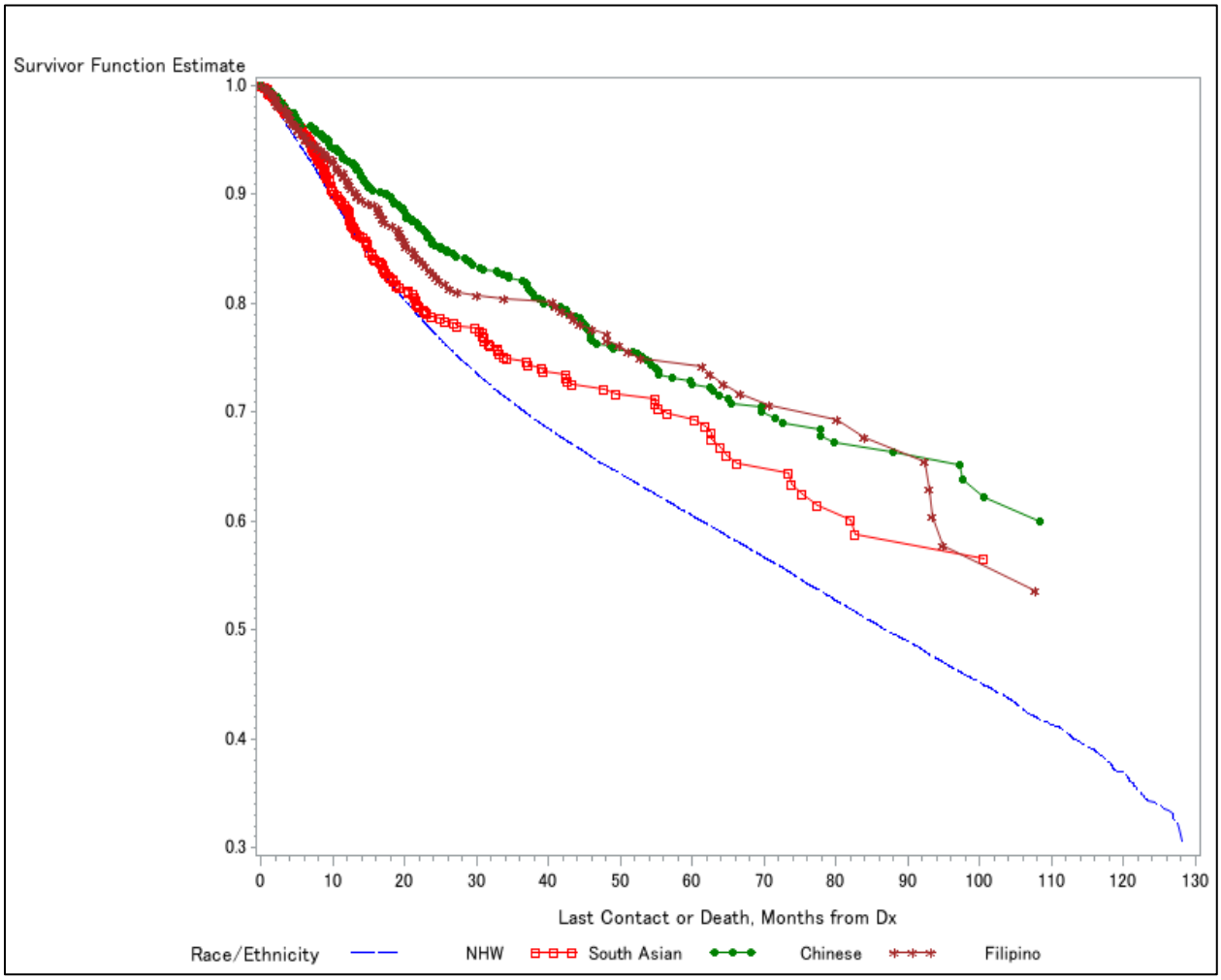
1. Kaplan Meier Estimates and Survival Differences

Overall survival differed by race/ethnicity (log rank p value<0.001). Figure 16 shows the survival over follow up time. The survival was better in all three Asian subgroups when compared to NHW but Chinese males fare best in survival consistently over time. Figure 16 (b) and 16 (c) show Kaplan Meier estimates that have been adjusted for age group, Charlson/Deyo comorbidity score, site group, insurance status, period of diagnosis, area level income, grade and spread. When Kaplan Meier survival estimates are broken down by stage at diagnosis, survival in South Asian I/P was slightly lower than NHW but was much lower than the other two Asian groups in cases with late stage diagnosis. When broken down by site group, survival was worst for South Asians among OPC cases. For Non-OPC, all three Asian subgroups had much better survival than NHW. Figure 17 shows the adjusted Kaplan Meier survival estimates for each racial/ethnic group by site group and stage. Figure 17 (a) and (b) were adjusted for site group along with other covariates including age group, comorbidity score, insurance status, period of diagnosis, area level income, grade and spread; 17 (c), (d), (e) and (f) were adjusted for all the covariates mentioned above. Figure 18 shows the unadjusted Kaplan Meier survival estimates by site group and stage.

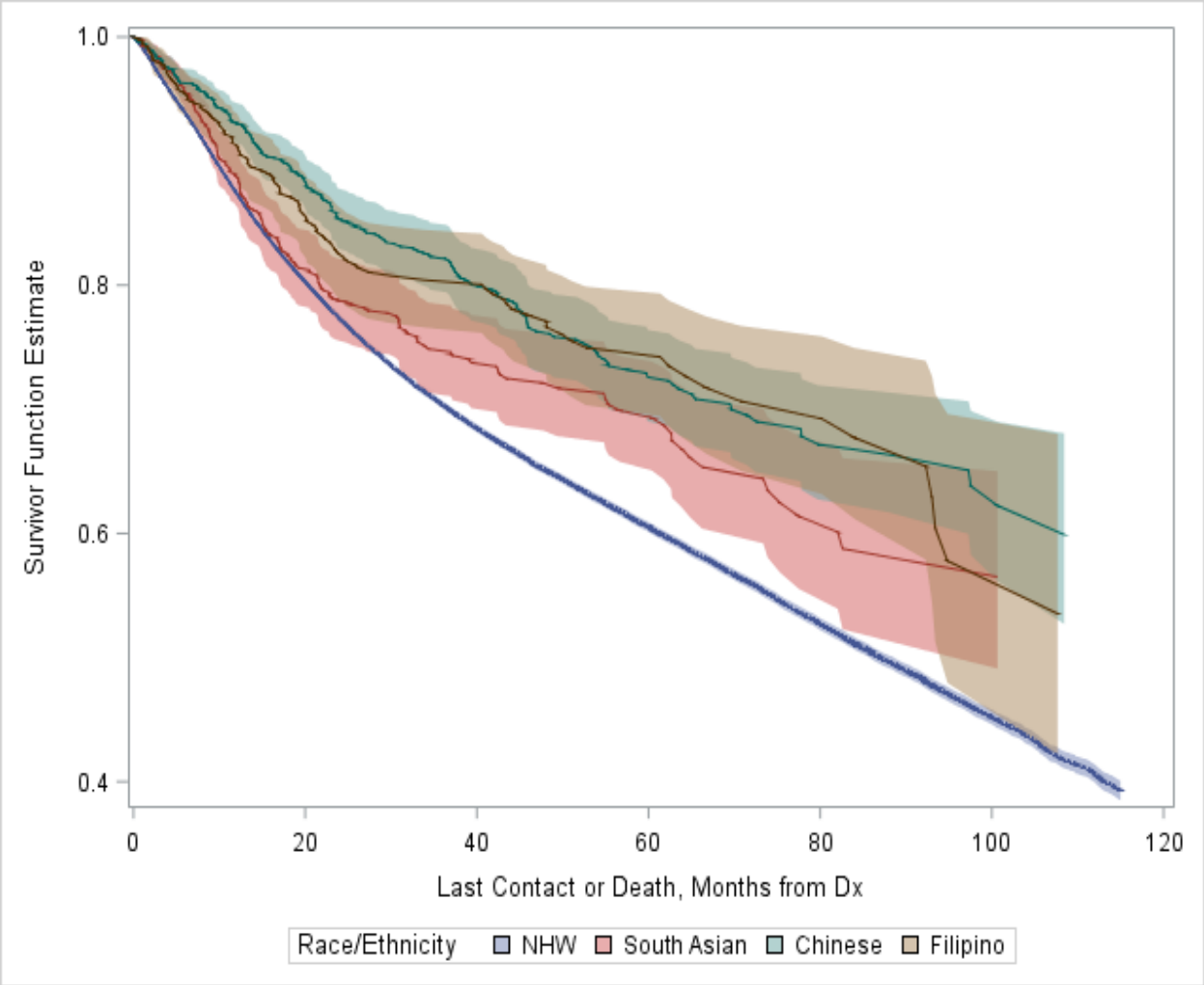
Figure 16: Kaplan Meier Estimates of overall survival by race/ethnicity, 2004 – 2012. 16a) Unadjusted; 16b) Adjusted; 16c) Adjusted estimates with 95% CI.


+ Censored
Logrank p <.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
25
50
75
100
125
Last Contact or Death, Months from Dx
Race
South Asian
Chinese
Filipino
NHW
South Asian 751 413 226 92 34 0
Chinese 928 624 372 174 62 2
Filipino 432 277 180 91 27 1
NHW 138060 85985 48678 23821 8322 404

16a.

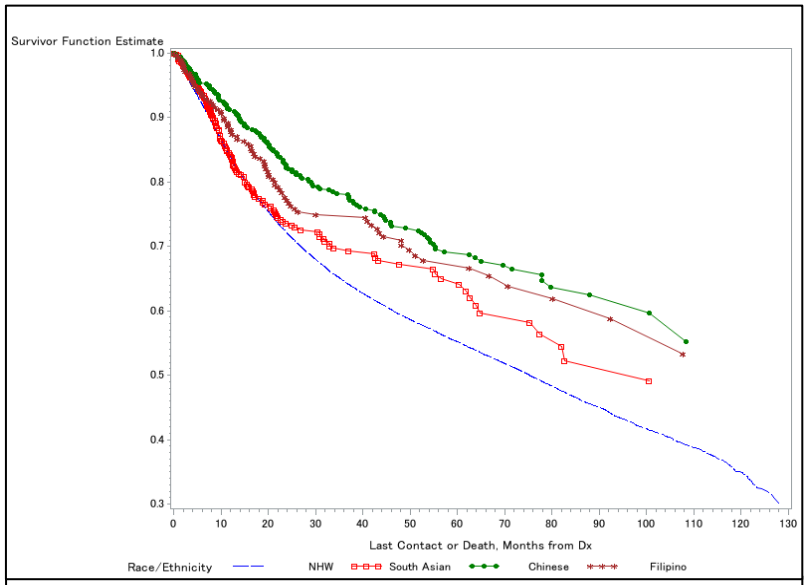

Survivor Function Estimate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0
10
20
30
40
50
60
70
80
90
100
110
120
130
Last Contact or Death, Months from Dx
Race/Ethnicity
NHW
South Asian
Chinese
Filipino

16b.

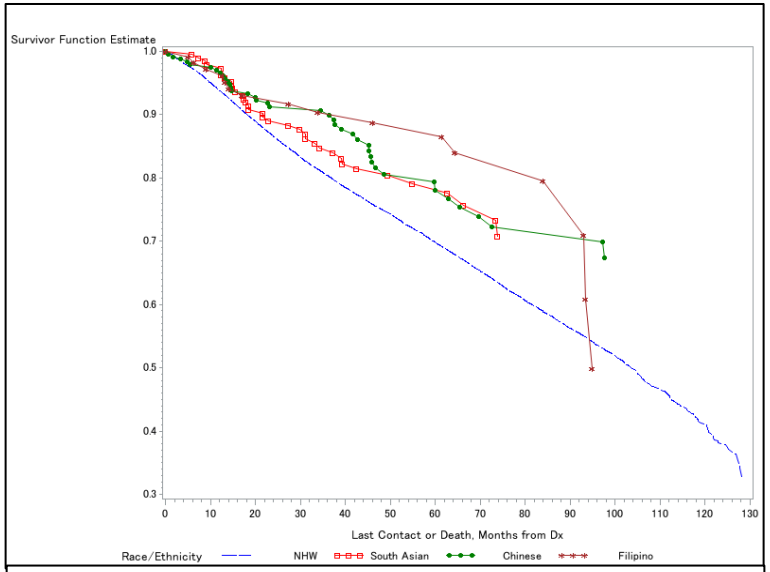

1.0
0.8
0.6
0.4
Survivor Function Estimate
0
20
40
60
80
100
120
Last Contact or Death, Months from Dx
Race/Ethnicity
NHW
South Asian
Chinese
Filipino

16c.

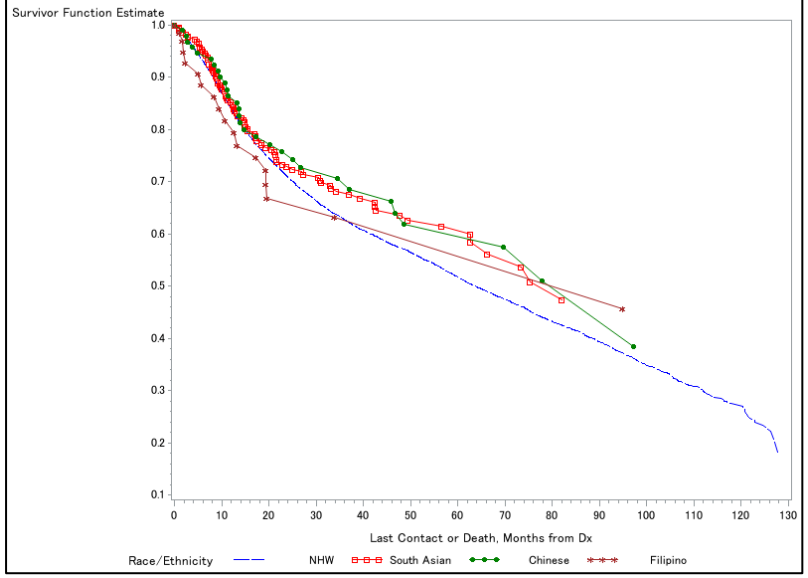
Figure 17: Adjusted Kaplan Meier survival estimates by race/ethnicity among male HNSCC cases with late stage (a), early stage (b), OCC (c), OPC (d), non-OPC (e), or laryngeal cancer (f) diagnosis



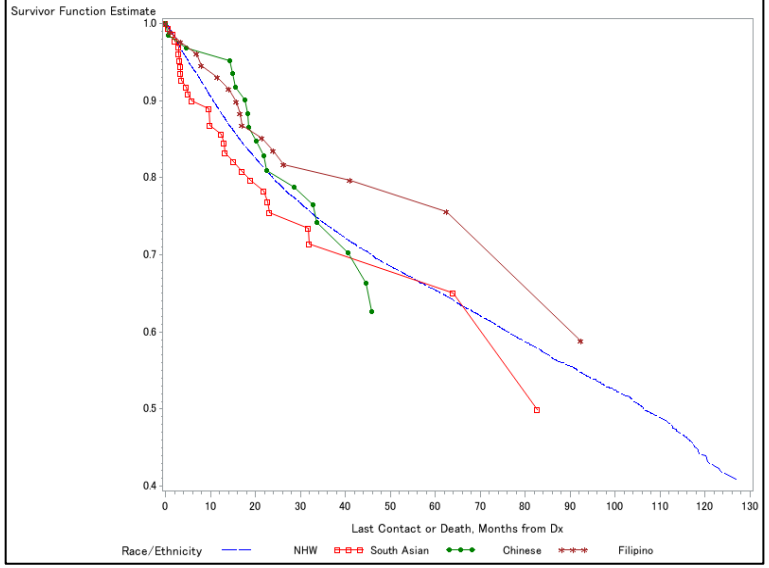
17a.



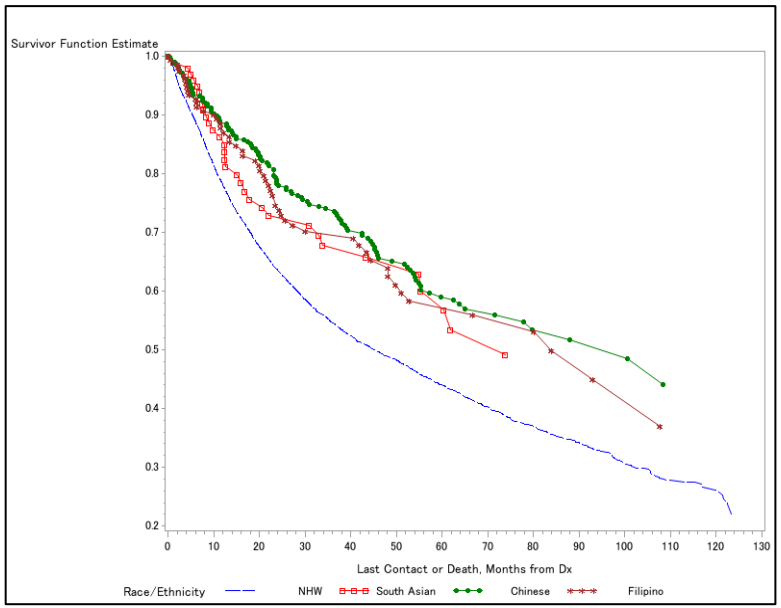
17b.



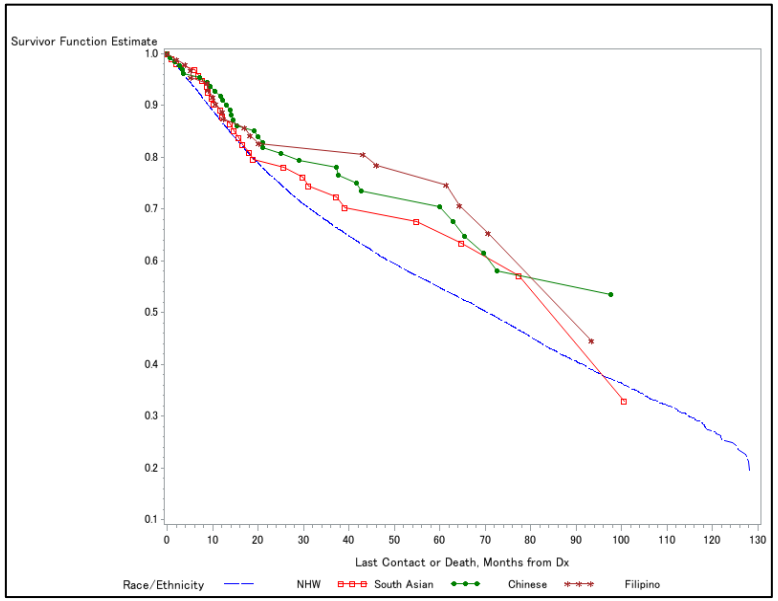
17c.



17d.

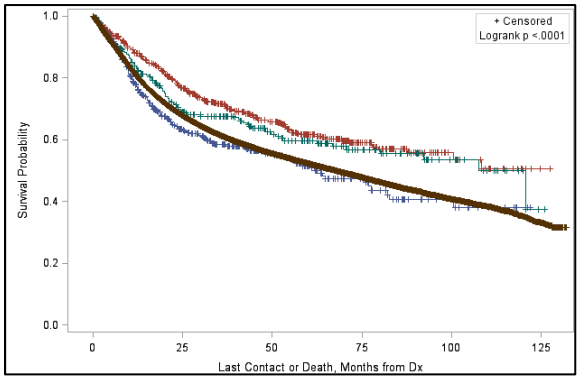

Survivor Function Estimate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0 10 20 30 40 50 60 70 80 90 100 110 120 130
Last Contact or Death, Months from Dx
Race/Ethnicity
NHW
South Asian
Chinese
Filipino

17e.

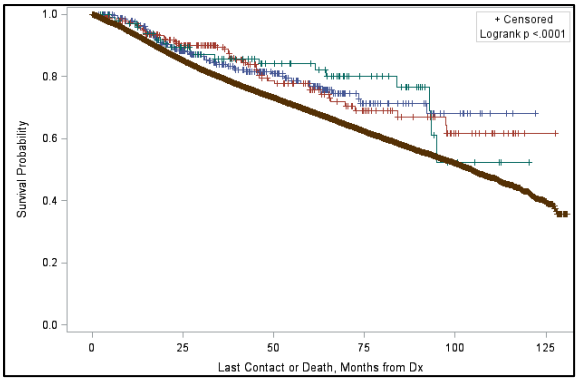

Survivor Function Estimate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0 10 20 30 40 50 60 70 80 90 100 110 120 130
Last Contact or Death, Months from Dx
Race/Ethnicity
NHW
South Asian
Chinese
Filipino

17f.

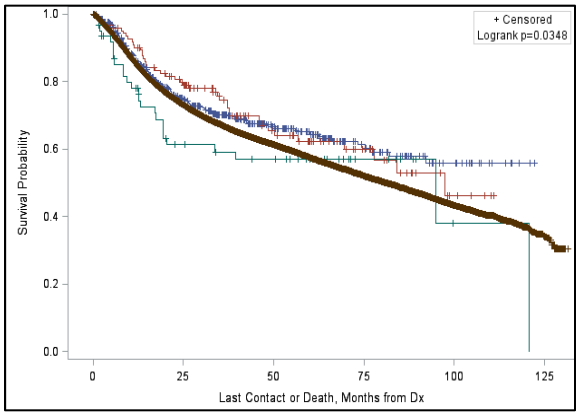
Figure 18: Unadjusted Kaplan Meier survival estimates by race/ethnicity among male HNSCC cases with late stage (a), early stage (b), OCC (c), OPC (d), non-OPC (e), or laryngeal cancer (f) diagnosis



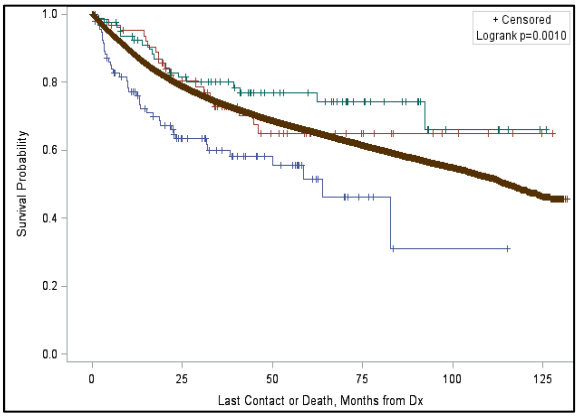
18a. Late stage



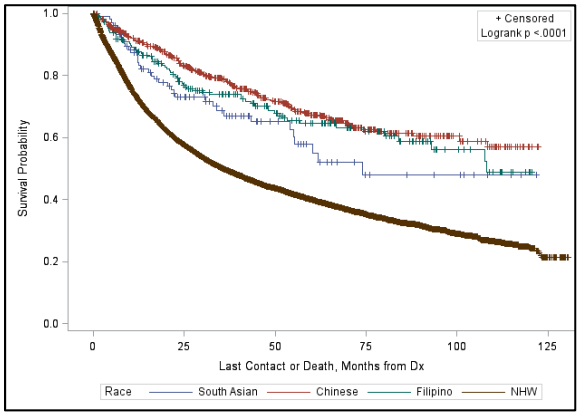
18b. Early stage



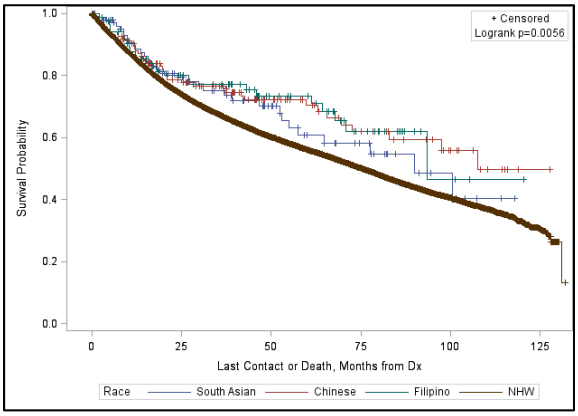
18c. Oral Cancer



18d. Oropharynx



18e. Non-oropharynx



18f. Larynx

2. Race/Ethnicity and All-Cause Mortality

In the crude analysis, Chinese (Hazard Ratio=0.70; 95% CI: 0.62 – 0.79) and Filipino (Hazard Ratio=0.76; 95% CI: 0.64 – 0.90) had lower hazards of mortality than NHW, while no difference was found for South Asian I/P. After adjusting for covariates (age, comorbidity score, site group, insurance, period of diagnosis, area-level income, grade and spread), all three Asian diasporas had lower hazards of mortality than NHW males. Chinese (Hazard Ratio=0.65; 95% CI: 0.56 – 0.76) and Filipino (Hazard Ratio=0.62; 95% CI: 0.50 – 0.77) male HNSCC cases had 35% and 38% lower hazard of dying, respectively, while South Asian I/P (Hazard Ratio=0.76; 95% CI: 0.64 – 0.89) cases had 24% lower hazard of dying than NHW males. Table XIII presents the crude and adjusted Hazard Ratios for race/ethnicity.

TABLE XIII

RESULTS OF MULTIVARIATE COX PROPORTIONAL HAZARDS MODEL FOR HAZARD OF DYING.

	Crude Hazard Ratio (95% CI)	Model 1[b] Adjusted Hazard Ratio (95% CI)	Model 2[c] Adjusted Hazard Ratio (95% CI)	Model 3[d] Adjusted Hazard Ratio (95% CI)	Model 4[e] Adjusted Hazard Ratio (95% CI)
Race					
Chinese	**0.70 (0.62 – 0.79)**	**0.65 (0.56 – 0.76)**	**0.71 (0.62 – 0.81)**	**0.59 (0.51 – 0.68)**	**0.62 (0.55 – 0.71)**
South Asian I/P	0.91 (0.81 – 1.04)	**0.76 (0.64 – 0.89)**	**0.82 (0.72 – 0.95)**	**0.79 (0.68 – 0.91)**	**0.84 (0.73 – 0.96)**
Filipino	**0.76 (0.64 – 0.90)**	**0.62 (0.50 – 0.77)**	**0.69 (0.57 – 0.83)**	**0.63 (0.52 – 0.77)**	**0.68 (0.57 – 0.80)**
NHW	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

[a] For the crude model, the number of deaths among Chinese=271, South Asian I/P=244, Filipino=137, NHW=54284.

[b] Model 1 was adjusted for age group, comorbidity score, site group, insurance status, period of diagnosis, area level income, grade and spread. (Note: all covariates except age were included in the strata). For this model, the number of deaths among Chinese=207, South Asian I/P=175, Filipino=105, NHW=41370.

[c] Model 2 represents all the variables in model 1 but spread was replaced by stage. For this model, the number of deaths among Chinese=260, South Asian I/P=223, Filipino=131, NHW=51373.

[d] Model 1 rerun with all the variables in the model statement (instead of strata).

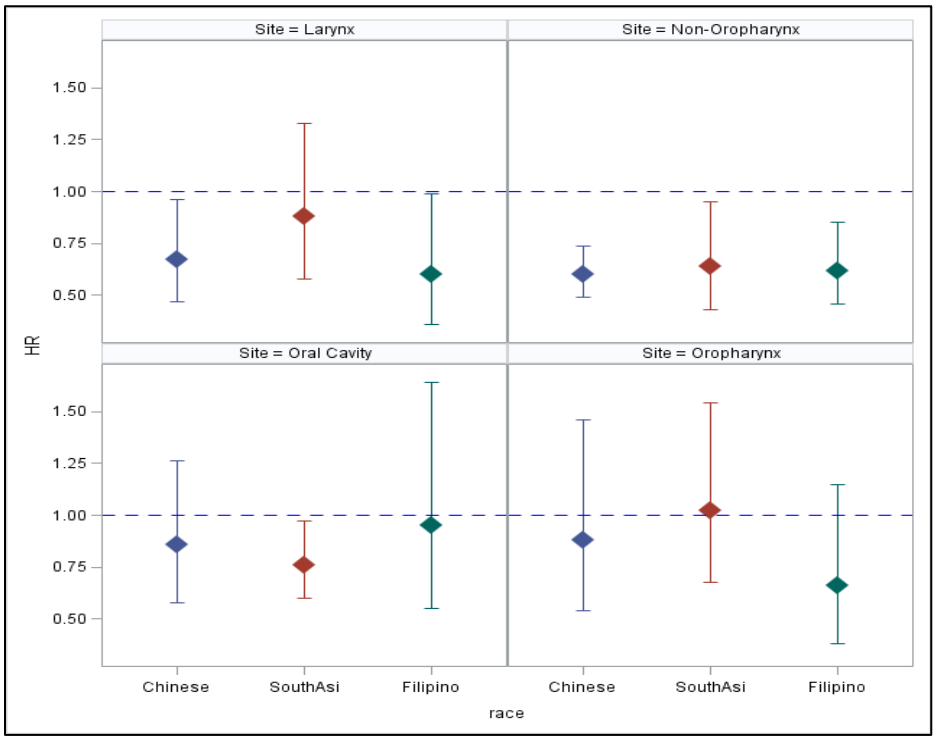
[e] Model 2 rerun with all the variables in the model statement (instead of strata).

These racial/ethnic differences became clearer when we further examined all-cause mortality by site group, stage, area level median household income and area level educational attainment (Figure 19). Among non-OPC cases, all three Asian subgroups had significantly lower mortality than NHW, while for OPC cases, no racial/ethnic difference was found in mortality (Figure 19). Among OCC cases, only South Asian I/P had significantly lower mortality compared to NHW. The most striking finding by stage was among Stage IV cancers, where all three Asian subgroups had lower mortality than NHW.

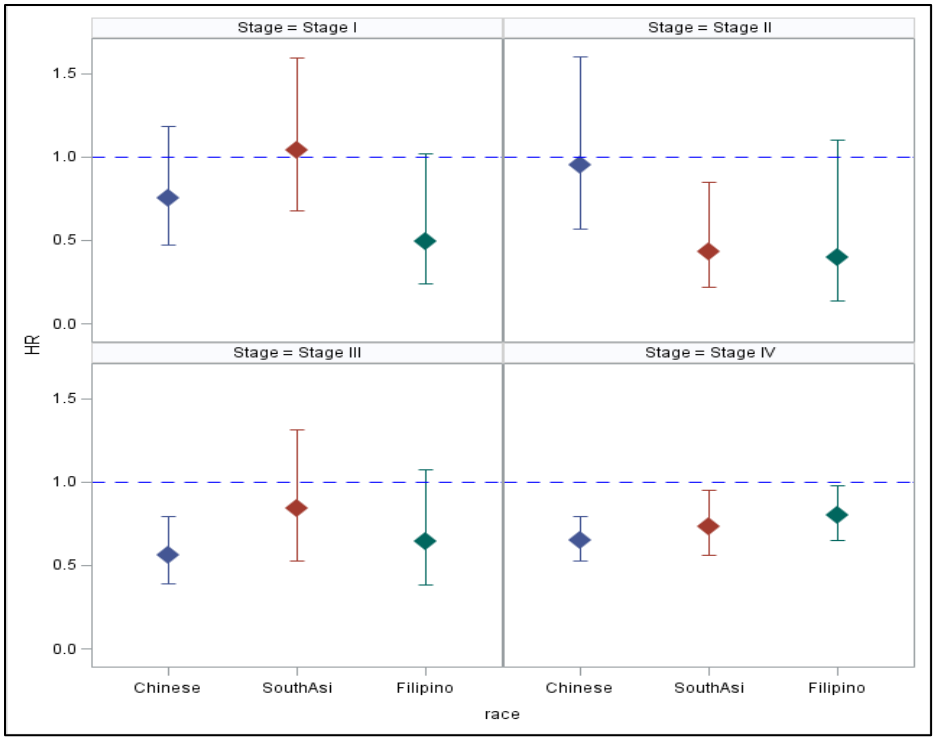
3. **Treatment Differences**

Of those for whom primary treatment was recorded, South Asian I/P males had higher likelihood of receiving surgical treatment with or without other treatments (65% vs. 26% in Chinese, 33% in Filipinos and 51% in NHW) when all HNSCC sites were examined together (Figure 20a), and when stratified by the stage at diagnosis (Figure 20b). Chemo-radiotherapy was more common in Chinese and Filipino males. However, the treatment differences between racial/ethnic groups were less pronounced when examined by site group in Figure 20c and Table XIV. Therefore, the overall difference in treatment by race/ethnicity could be partly explained by differences in distribution of site group. As shown in Table XIV, radiotherapy (with or without Chemotherapy) was the most common treatment for nasopharyngeal cancers among all the racial/ethnic groups; however, strikingly, NHW had a slightly higher proportion of surgically treated (with or without radio- and/or chemotherapy) cases than the Asian subgroups.

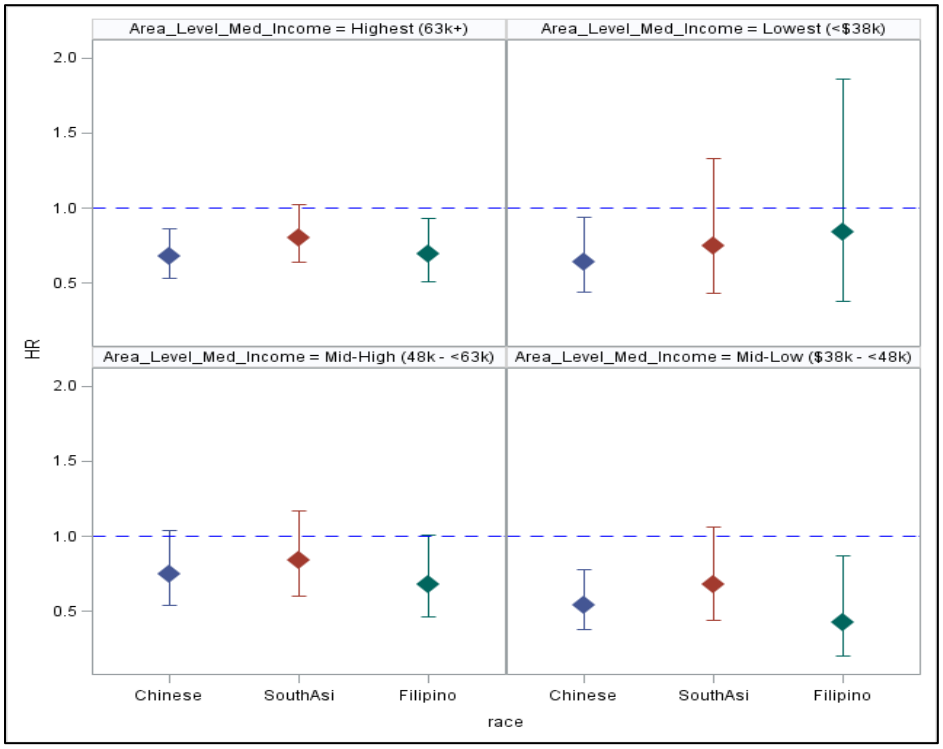
Figure 19: Hazard Ratios (with 95% CI) for the association of race/ethnicity with mortality stratified by tumor site group (a), stage at diagnosis (b), area level median household income (c) and area level educational attainment (d)


Site = Larynx
Site = Non-Oropharynx
Site = Oral Cavity
Site = Oropharynx
HR
1.50
1.25
1.00
0.75
0.50
Chinese
SouthAsi
Filipino
race

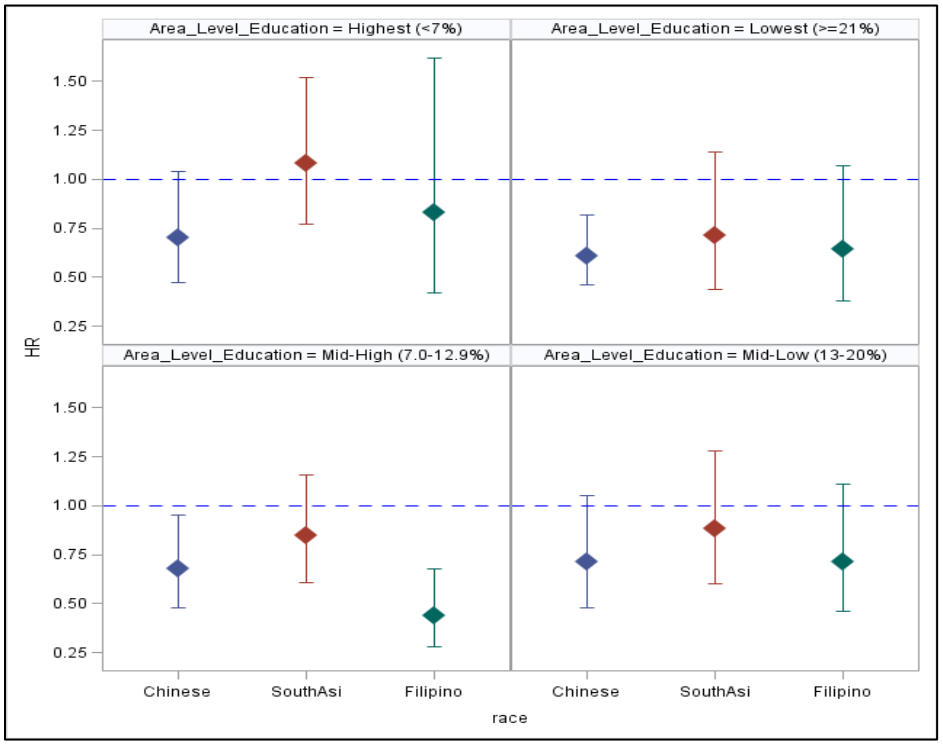
19a.


Stage = Stage I
Stage = Stage II
Stage = Stage III
Stage = Stage IV
HR
1.5
1.0
0.5
0.0
Chinese
SouthAsi
Filipino
race

19b.

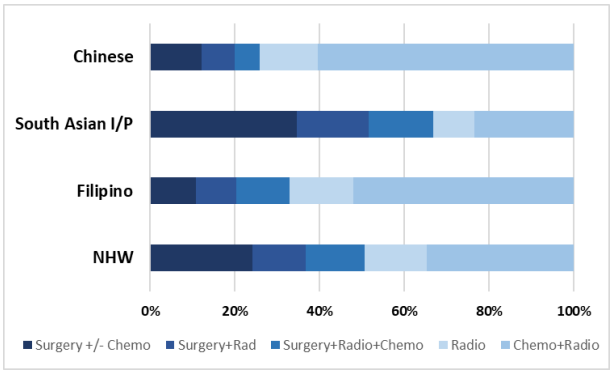

Area_Level_Med_Income = Highest (63k+)
Area_Level_Med_Income = Lowest (<$38k)
Area_Level_Med_Income = Mid-High (48k - <63k)
Area_Level_Med_Income = Mid-Low ($38k - <48k)
HR
2.0
1.5
1.0
0.5
Chinese
SouthAsi
Filipino
race

19c.

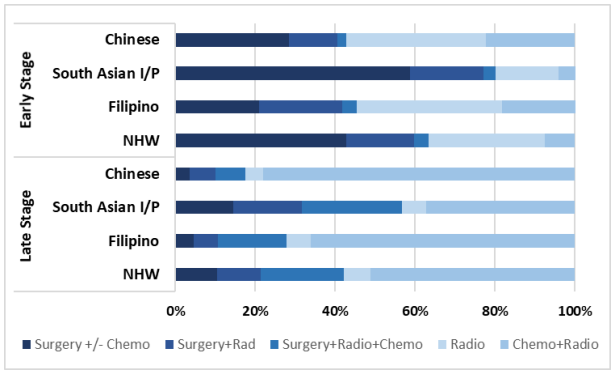

Area_Level_Education = Highest (<7%)
Area_Level_Education = Lowest (>=21%)
Area_Level_Education = Mid-High (7.0-12.9%)
Area_Level_Education = Mid-Low (13-20%)
HR
1.50
1.25
1.00
0.75
0.50
0.25
Chinese
SouthAsi
Filipino
race

19d.

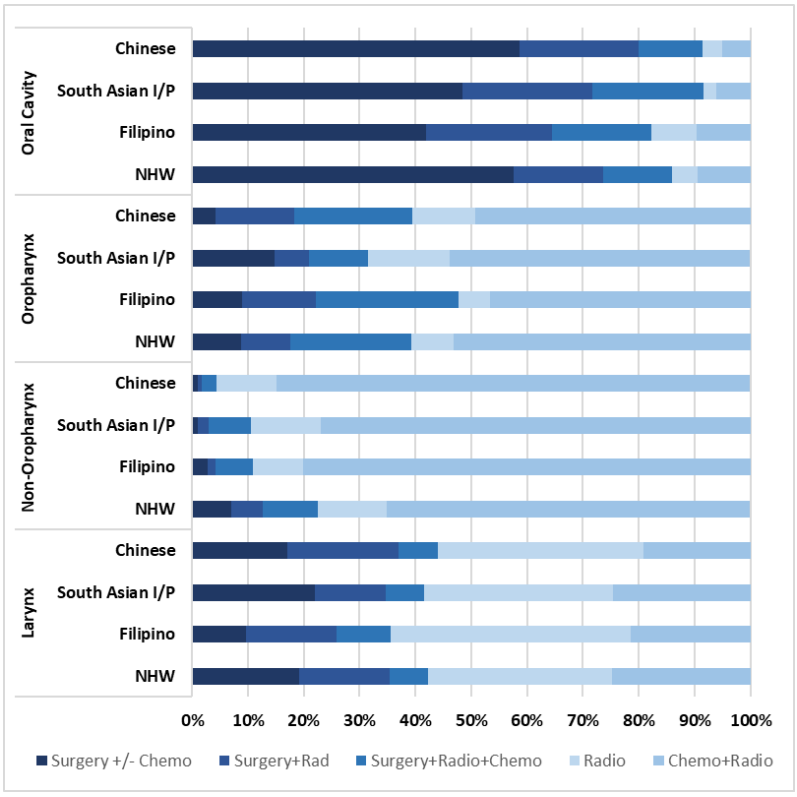
Figure 20: Treatment type by race/ethnicity (a), race/ethnicity and stage at diagnosis (b), and race/ethnicity and tumor site grouping (c)



20a. Treatment type by race/ethnicity



20b. Treatment type by race/ethnicity and stage



20c. Treatment type by race/ethnicity and tumor site group.

TABLE XIV

TREATMENT BY HEAD AND NECK CANCER SITE (AND HPV STATUS FOR OROPHARYNGEAL SITE) AND BY RACE/ETHNICITY

		Surgery	Radiotherapy	Chemotherapy	Surgery + Rad	Surgery + Chemo	Rad + Chemo	All three
Lip	**Chinese**	-	-	-	1 (100%)	-	-	-
	South Asian I/P	8 (72.7%)	-	-	1 (9.1%)	-	-	2 (18.2%)
	Filipino	-	-	-	1 (100%)	-	-	-
	NHW	3858 (85.1%)	180 (4.0%)	10 (0.2%)	343 (7.6%)	22 (0.5%)	29 (0.6%)	90 (2.0%)
Oral Cavity	**Chinese**	67 (53.2%)	4 (3.2%)	3 (2.4%)	28 (22.2)	2 (1.6%)	6 (4.8%)	16 (12.7%)
	South Asian I/P	195 (46.5%)	8 (1.9%)	3 (0.7%)	92 (22.0)	7 (1.7%)	29 (6.9%)	85 (20.3%)
	Filipino	25 (42.4%)	5 (8.5%)	-	14 (23.7%)	-	6 (10.2%)	9 (15.2%)
	NHW	18164 (55.6%)	1511 (4.6%)	422 (1.3%)	5249 (16.1%)	299 (0.9%)	3125 (9.6%)	3897 (11.9%)
Oropharynx – HPV positive	**Chinese**	-	1 (14.3%)	-	-	-	4 (57.1%)	2 (28.6%)
	South Asian I/P	-	-	-	-	-	2 (66.7%)	1 (33.3%)
	Filipino	-	-	-	1 (100%)	-	-	-
	NHW	323 (7.6%)	174 (4.1%)	54 (1.3%)	453 (10.6%)	29 (0.7%)	2090 (49.1%)	1130 (26.6%)
Oropharynx – HPV negative	**Chinese**	1 (12.5%)	1 (12.5%)	-	-	-	3 (37.5%)	3 (37.5%)
	South Asian I/P	-	-	1 (11.1%)	-	-	5 (55.6%)	3 (33.3%)
	Filipino	1 (12.5%)	-	-	1 (12.5%)	-	2 (25.0%)	4 (50.0%)
	NHW	405 (7.8%)	276 (5.3%)	127 (2.5%)	417 (8.1%)	43 (0.8%)	2609 (50.5%)	1292 (25.0%)
Hypopharynx	**Chinese**	1 (3.8%)	2 (7.7%)	2 (7.7%)	-	-	18 (69.2%)	3 (11.5%)
	South Asian I/P	1 (2.4%)	7 (16.7%)	4 (9.5%)	-	-	27 (64.3%)	3 (7.1%)
	Filipino	2 (10.5%)	3 (15.8%)	1 (5.3%)	-	-	8 (42.1%)	5 (26.3%)
	NHW	376 (6.4%)	731 (12.4%)	335 (5.7%)	393 (6.6%)	48 (0.8%)	3428 (57.9%)	609 (10.3%)
Nasopharynx	**Chinese**	4 (0.8%)	58 (11.0%)	15 (2.9%)	4 (0.8%)	1 (0.2%)	432 (82.3%)	11 (2.1%)
	South Asian I/P	-	4 (7.1%)	3 (5.4%)	2 (3.6%)	-	45 (80.4%)	2 (3.6%)
	Filipino	3 (1.8%)	13 (7.7%)	4 (2.4%)	2 (1.2%)	1 (0.6%)	138 (82.1%)	7 (4.2%)
	NHW	119 (3.5%)	280 (8.3%)	191 (5.7%)	108 (3.2%)	22 (0.6%)	2381 (70.7%)	268 (8.0%)
Larynx	**Chinese**	21 (16.8%)	47 (37.6%)	1 (0.8%)	22 (17.6%)	-	25 (20.0%)	9 (7.2%)
	South Asian I/P	19 (18.6%)	37 (36.3%)	-	12 (11.8%)	1 (1.0%)	26 (25.5%)	7 (6.9%)
	Filipino	5 (6.2%)	33 (41.2%)	-	15 (18.8%)	1 (1.2%)	18 (22.5%)	8 (10.0%)
	NHW	6814 (18.1%)	12255 (32.5%)	684 (1.8%)	6114 (16.2%)	204 (0.5%)	9099 (24.2%)	2513 (6.7%)

D. **Discussion**

Overall survival was better in HNSCC cases from these three Asian diasporas; however, Chinese males fare best in survival consistently over time, which was expected because out of the three Asian groups, only Chinese had significantly lower odds of late stage diagnosis, as observed in Aim 2. Certain factors, such as better overall health and younger age at diagnosis, may contribute to lower mortality in Asian subgroups but the differences remain even after adjusting for age group, Charlson/Deyo comorbidity score, site group, insurance status, period of diagnosis, area level income, grade and stage. This suggests that there are other factors that are probably contributing to the difference in mortality and survival. We did not have risk factor data, other than HPV (albeit with high proportion of unknown), therefore, we could not fully control for it, which may have contributed to the difference. Since HPV related OPCs are known to have better prognosis, and HPV was less common in two of the three Asian groups, the survival should have been poorer in those Asian subgroups. This was a paradoxical finding. Since HPV has a predilection for oropharyngeal sites, we further examined OPC cases, and there was no significant difference in mortality in Asian subgroups and NHW, when adjusted for covariates. However, significantly lower mortality in Asian subgroups was noticed among other site groups. When survival was examined, South Asians I/P with OPC had poorer survival over time when compared to the other Asian groups and NHW.

When treatment was compared across the racial/ethnic groups, a difference was noticed in treatment of nasopharyngeal cancer. Surgery is not commonly done in nasopharyngeal cancer cases (American Cancer Society, 2018.; National Comprehensive Cancer Network, 2019), and this was evident in our sample. However, NHW had a higher proportion of surgically treated (with or without radiotherapy and chemotherapy) cases than the Asian subgroups. This is

consistent with the findings reported by Wang et al. 2013, and this difference could potentially be due to recurrent cancers (Wang, Zhang, & Ma, 2013).

Asian subgroups had a remarkably lower mortality among stage IV HNSCCs. This is a key finding. Asians in the US are known to have higher life expectancy than Whites as they outlive Whites irrespective of the cause of death (Acciai, Noah, & Firebaugh, 2015). Multiple factors could be contributing to this lower mortality. Cultural factors, such as social support, especially in the form of spousal support, may play a role in improving survival and reducing mortality. Marital status has been shown to be an independent predictor of survival (Ikeda et al., 2007; Kaplan & Kronick, 2006) and a strong survival advantage has been found to be associated with being married in HNSCC (Inverso et al., 2015; Shi, Zhang, Hu, & Ji, 2017) and other cancer patients (Zhang, Qing-Wei et al., 2017; Zhang, Wenjie et al., 2017). Asian Americans have a higher likelihood of being currently married when compared to the overall US adult population (Pew Research Center, 2019), which could be playing a role in better survival observed in Asian diasporas in our study. Another likely reason is that Asian cases may move back to their native country after the diagnosis; therefore, under-reporting of death. Moreover, even though we accounted for severity of comorbidities with Charlson/Deyo comorbidity score, it is possible that we could not fully control for differences in overall health as it is hard to measure. Asians in the US are more likely to be first generation migrants (Pew Research Center, 2019); therefore, healthy migrant effect may contribute to better overall health in even those that had HNSCC.

Survival in these Asian diasporas cannot be fully attributed to better access to care and higher SES. Even though the likelihood of private insurance was slightly higher in the Asian groups, the likelihood of having no insurance and Medicaid insurance was also higher, when

compared to NHW. The effect of SES is harder to disentangle, considering we had only area level indicators and although the Asian groups had a higher likelihood of being in the highest quartile of area-level median household income, they were also more likely to be in the lowest quartile of area level educational attainment.

Younger age at diagnosis, especially the higher proportion of cases diagnosed by age 40 (and age 50) years and the lower mean age among Chinese cases reminds of a similar pattern seen in HPV-associated OPC among NHW males. Even though HPV 16/18 positive OPCs were less likely in two Asian subgroups, another virus, namely Epstein Barr virus may be playing a role in diagnosis at a younger age. This explanation is highly plausibly, considering Chinese were much more likely to have an undifferentiated tumor grade, and have nasopharyngeal cancers, both of which are associated with EBV (Thompson & Kurzrock, 2004).

A limitation of this study is that we used all-cause mortality instead of cause specific mortality. Another limitation is that we did not have any information on risk factors, such as smoking, alcohol use and areca nut use, that can have an impact on survival. Moreover, we do not have information on recurrence and relapse, which can also affect survival. Another limitation is that we did not have individual level SES indicators; however, we had area-level indicators which can serve as proxies for individual level SES.

A strength of this study is that we have a relatively large sample size of specific subpopulations which is not available in most other registries. NCDB has four times more cases than SEER; therefore, it is better in studying subpopulations that have a relatively small number of cases. Another strength is that this study addresses an important gap in the literature. Survival

has not been studied in these subpopulations in the US, even though we know that the mortality associated with certain specific HNSCCs is very high in Asian countries.

E. **Conclusion**

Since HNSCCs in Asian populations tend to be diagnosed at a younger age and tend to have better survival, we need to further study the impact of treatment on the quality of life. As Asian subgroups are less likely to be HPV 16/18 positive, the next step after this study will be to identify risk factors prevalent in Asian diasporas, which include smokeless tobacco and areca nut (with or without tobacco) chewing, to fully understand the impact of habits that are possibly causing cancer at an early age. We also need to further study the impact of risk factors on survival.

VI. OVERARCHING IMPLICATIONS

In our study, we found certain HNSCC site groups and distinct subsites to be much more common in specific subpopulations; such as, OCC (specifically the cancer of gum, buccal mucosa and other mouth) in South Asian I/P males and non-OPC (specifically, the cancer of nasopharynx) in Chinese males. These diasporas have been studied in their native Asian countries but not as much in the US. Knowing that some of these minority racial/ethnic groups are among the fastest growing subpopulations in the US, it is important to study these groups with respect to specific HNSCCs and their corresponding risk factors. As a next step, it is imperative to explore risk factors in these specific subpopulations in the US, especially those risk factors that are contributing to diagnosis at an early age, so that appropriate interventions can be designed.

As tobacco use has decreased in the US, there are other risk factors, apart from HPV, that are propelling the high rates of certain HNSCCs in certain groups. After risk factors are identified and their burden is quantified, policy changes need to be recommended to limit the access to certain risk factors, such as areca nut, especially among youth. Areca nut is an independent carcinogen (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2004) but is freely available in the US. It is consumed as a mouth freshener by certain diasporas (Aziz, 2010) and is erroneously, considered harmless; possibly contributing to early initiation of use (Auluck et al., 2009). Certain policy changes that either limit the access or increase awareness among high-risk populations need to be considered. Another key area is to study the impact of migration on the risk of HNSCCs and the risk factors associated with it by comparing native born cases to foreign born cases to better understand the effect of environment and early life influences.

Future studies should also examine rate of HNSCC screening in minority racial/ethnic groups. While OCC is easy to screen with a non-invasive visual-tactile screening, it is not common in the majority of the US population, and screening is not recommended in normal healthy adults (US Preventive Services Task Force, 2013). However, based on our findings, South Asians can be considered a high-risk population for OCC; therefore, screening should be promoted in these subpopulations. Similarly, nasopharyngeal cancer screening should be promoted among Chinese (and Filipinos, to some extent). Primary care practitioners (PCP) and dental practitioners can play a major role in this. Although dentists are more likely to examine the oral cavity and come across pre-malignant and malignant lesions of the mouth, minority groups may be less likely to have dental insurance; thereby, not have access to a dentist. For certain minority groups, PCP may be their only point of access to care. Therefore, PCPs need to be aware of higher risk in distinct subpopulations and should look for signs of premalignancy and malignancy in their patients from minority groups. If there are any barriers to access screening, then those should also be studied in these populations with qualitative methods. Policy makers should also consider recommending specific HNSCC screenings for certain minority groups.

Our findings hinted towards a correlation between HPV unknown status and SES; where higher the SES, lower is the probability of having unknown HPV status (among OPC cases). This association needs to be studied further, especially since it is known that HPV positive tumors respond differently to treatment and have better prognosis. Our prior work on NHB and NHW (Peterson et al., 2017) has shown that economic advantage is associated with a higher risk of HPV positive tumors. So, our next step would be to understand the predictors of HPV unknown status and assess the independent effect of SES on HPV testing. Although a new

staging system has been designed for HPV positive tumors (American College of Surgeons, 2018), the correct stage cannot be determined if HPV status is unknown.

Future research studies should also examine HNSCCs in females, especially those of minority groups. Data from more years may have to be combined to increase the sample and have enough power to explore specific site groups, subsites and HPV status in females. Although salivary gland tumors are rare and are typically non-squamous (Boukheris et al., 2009), future research studies should also explore salivary gland tumor risk in minority racial/ethnic groups to see if certain groups have higher risk than others, provided enough number of cases can be recruited in the study.

Our future research may also extend the work done in three largest Asian subpopulations to other Asian, Pacific Islander and Hispanic groups to better understand the differences among these heterogeneous groups and identify other high-risk subpopulations.

APPENDICES

Appendix A
HNSCCs among the largest Hispanic groups in the US

TABLE XV
COMPARISON OF PATIENT CHARACTERISTICS IN MEXICAN, CUBAN AND PUERTO RICAN MALES IN THE US WITH NHW MALES, 2004 – 2013

	Mexican males N=1204 Mean [SD] or n (%)	Cuban males N=762 Mean [SD] or n (%)	Puerto Rican males N=567 Mean [SD] or n (%)	NHW males N=156927 Mean [SD] or n (%)	p-value
Age at diagnosis					
Mean years [SD]	59.5 [13]	62.8 [11]	62.5 [11]	61 [11]	<0.0001
Age group					
≤40	69 (5.7%)	17 (2.2%)	10 (1.8%)	4009 (2.6%)	<0.0001
41-50	210 (17.4%)	81 (10.6%)	67 (11.8%)	22852 (14.6%)	
51-60	382 (31.7%)	235 (30.8)	172 (30.3%)	53306 (34.0%)	
61-70	300 (24.9%)	244 (32.0)	188 (33.2%)	44806 (28.6%)	
>70	243 (20.2%)	185 (24.3%)	130 (22.9%)	31954 (20.4%)	
Period of Diagnosis					<0.0001
Pre ACA (2004-10)	825 (68.5%)	581 (76.2%)	402 (70.9%)	103468 (65.9%)	
Post ACA (2011-13)	379 (31.5%)	181 (23.8%)	165 (29.1%)	53459 (34.1%)	
Insurance					<0.0001
Private	331 (28.7%)	191 (25.3%)	134 (24.0%)	71180 (46.9%)	
Other Govt	13 (1.1%)	5 (0.7%)	7 (1.2%)	3782 (2.5%)	
Medicare	348 (30.2%)	247 (32.7%)	252 (45.1%)	55382 (36.5%)	
Medicaid	280 (24.3%)	202 (26.7%)	144 (25.8%)	12576 (8.3%)	
No Insurance	180 (15.6%)	111 (14.7%)	22 (3.9%)	8959 (5.9%)	
Area-level Median Household Income					<0.0001
$63,000+	214 (18.1%)	65 (8.7%)	105 (18.8%)	46195 (29.9%)	
$48,000-$62,999	314 (26.5%)	186 (24.8%)	137 (24.6%)	42688 (27.6%)	
$38,000-$47,999	319 (26.9%)	167 (22.3%)	114 (20.5%)	39764 (25.8%)	
<$38,000	338 (28.5%)	331 (44.2%)	201 (36.1%)	25731 (16.7%)	
Area-level educational attainment (% with No HSD)					<0.0001
<7%	92 (7.7%)	25 (3.3%)	40 (7.2%)	35794 (23.2)	
7-12.9%	150 (12.6%)	72 (9.6%)	101 (18.1%)	52573 (34.0)	
13-20%	208 (17.5%)	207 (27.6%)	142 (25.4%)	42266 (27.4)	
>=21%	738 (62.1%)	445 (59.4%)	275 (49.3%)	23839 (15.4)	

Appendix A (Continued)
HNSCCs among the largest Hispanic groups in the US (Continued)

TABLE XV (Continued)
COMPARISON OF PATIENT CHARACTERISTICS IN MEXICAN, CUBAN AND PUERTO RICAN MALES IN THE US WITH NHW MALES, 2004 – 2013

	Mexican males N=1204 Mean [SD] or n (%)	Cuban males N=762 Mean [SD] or n (%)	Puerto Rican males N=567 Mean [SD] or n (%)	NHW males N=156927 Mean [SD] or n (%)	p-value
Subsite of Tumor					<0.0001
Lip	53 (4.4%)	22 (2.9%)	5 (0.9%)	5147 (3.3)	
Gum/FOM/OtherM	195 (16.2%)	88 (11.6%)	93 (16.4%)	18702 (11.9)	
Tongue (Anterior)	107 (8.9%)	63 (8.3%)	47 (8.3%)	14736 (9.4)	
Tongue (Base)	109 (9.1%)	76 (10.0%)	60 (10.6%)	24295 (15.5)	
Tonsil	140 (11.6%)	115 (15.1%)	85 (15.0%)	28313 (18.0)	
Oropharynx	38 (3.2%)	22 (2.9%)	27 (4.8%)	5894 (3.8)	
Nasopharynx	64 (5.3%)	29 (3.8%)	28 (4.9%)	4194 (2.7)	
Hypopharynx	84 (7.0)	33 (4.3%)	42 (7.4%)	7511 (4.8)	
Other Pharynx	11 (0.9%)	6 (0.8%)	10 (1.8%)	1926 (1.2)	
Larynx	403 (33.5%)	308 (40.4%)	170 (30.0%)	46209 (29.4)	
Site group					<0.0001
Oral Cavity	355 (29.5%)	173 (22.7%)	145 (25.6%)	38585 (24.6)	
Oropharynx	287 (23.8%)	213 (28.0%)	172 (30.3%)	58502 (37.3)	
Non-Oropharynx	159 (13.2%)	68 (8.9%)	80 (14.1%)	13631 (8.7)	
Larynx	403 (33.5%)	308 (40.4%)	170 (30.0%)	46209 (29.4)	
HPV status (for all cases)					<0.0001
HPV 16/18 positive	19 (1.6%)	15 (2.0%)	10 (1.8%)	8040 (5.1)	
HPV 16/18 negative	93 (7.7%)	90 (11.8%)	64 (11.3%)	16221 (10.3)	
HPV unknown	1092 (90.7%)	657 (86.2%)	493 (87.0)	132666 (84.5)	
HPV status (for 2009 - 2013 cases only)					<0.0001
HPV 16/18 positive	19 (3.0%)	15 (4.2%)	10 (3.6%)	8037 (9.4)	
HPV 16/18 negative	91 (14.3%)	90 (25.1%)	63 (22.5%)	16119 (18.8)	
HPV unknown	525 (82.7%)	254 (70.8%)	207 (73.9%)	61766 (71.9)	

Appendix B
HPV status for all HNSCC sites combined

TABLE XVI
DISTRIBUTION OF HPV STATUS AMONG MALE HNSCC CASES FROM VARIOUS RACIAL/ETHNIC GROUPS USING NATIONAL CANCER DATABASE

	NHW Males	NHB Males	Hispanic[a] Males	American Indian Males	Asian Males	Pacific Islander Males
HPV status[b] (for all sites, 2004 - 2013)						
HPV 16/18 positive	8040 (5.1)	428 (2.0)	239 (2.7)	17 (2.8)	80 (1.9)	11 (4.4)
HPV 16/18 negative	16221 (10.3)	1956 (9.2)	835 (9.4)	62 (10.3)	470 (10.9)	18 (7.2)
HPV unknown	132666 (84.5)	18995 (88.8)	7787 (87.9)	524 (86.9)	3758 (87.2)	220 (88.4)
HPV status[b] (all sites, 2009 - 2013)						
HPV 16/18 positive	8037 (9.4)	428 (4.9)	239 (5.0)	17 (4.8)	80 (3.3)	11 (7.1)
HPV 16/18 negative	16119 (18.8)	1945 (17.4)	829 (17.2)	62 (17.5)	467 (19.3)	18 (11.7)
HPV unknown	61766 (71.9)	8816 (78.8)	3744 (77.8)	276 (77.8)	1877 (77.4)	125 (81.2)

[a] Includes Hispanic Whites and Blacks only.

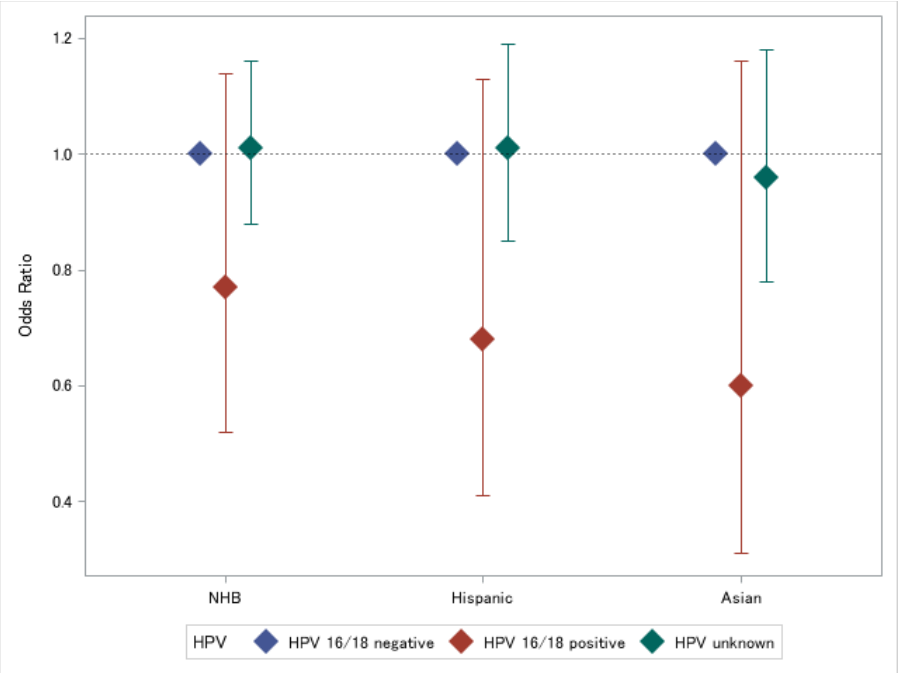
[b] HPV 16/18 positive represents cases that were positive for HPV 16 or HPV 18 or both, HPV 16/18 negative represents cases that were negative for both HPV 16 and 18 but could be positive for HPV types other than 16/18 (includes “HPV negative for high-risk and low-risk types, HPV negative for high-risk types with no mention of low-risk types, Negative NOS”, “HPV positive for low-risk types only”, “HPV positive for specified high risk type(s) other than types 16 or 18”, “HPV positive for high-risk type(s), NOS, high-risk type(s) not stated”, HPV positive NOS risk and type(s) not stated”) and HPV unknown includes “Not applicable: Information not collected for this case”, “Test ordered, results not in chart”, “Test not done (test was not ordered and was not performed), including no pathologic specimen available for HPV testing”, “Unknown or no information” ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.)

Appendix C

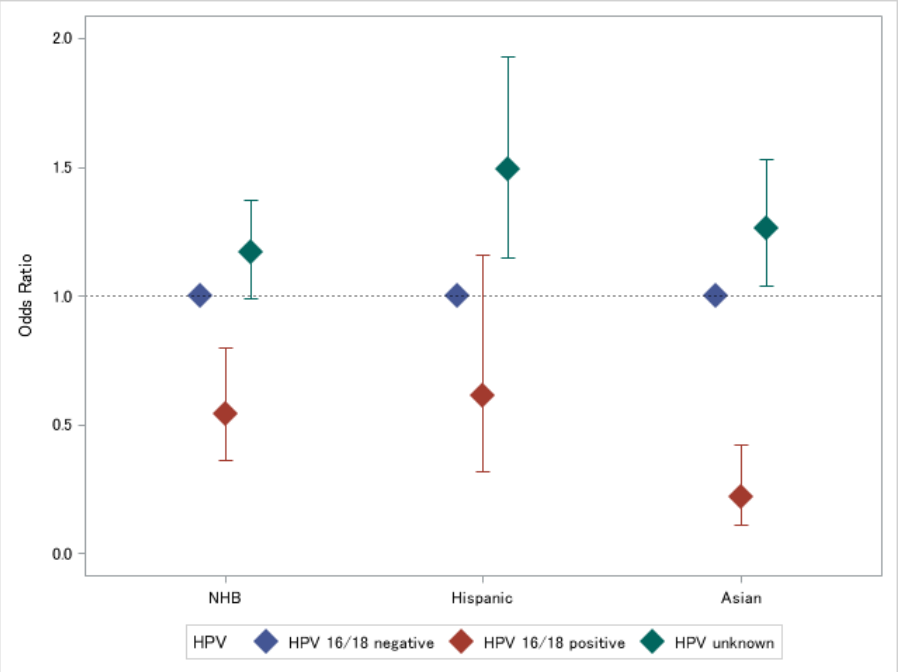
Association of race/ethnicity with HPV status by site group - other than Oropharynx

Figure 21: Association of race/ethnicity with HPV status by tumor site group other than Oropharynx; a) Oral Cavity, b) Non-oropharynx, c) Larynx.

Appendix C (Continued)
Association of race/ethnicity with HPV status by site group - other than Oropharynx (Continued)

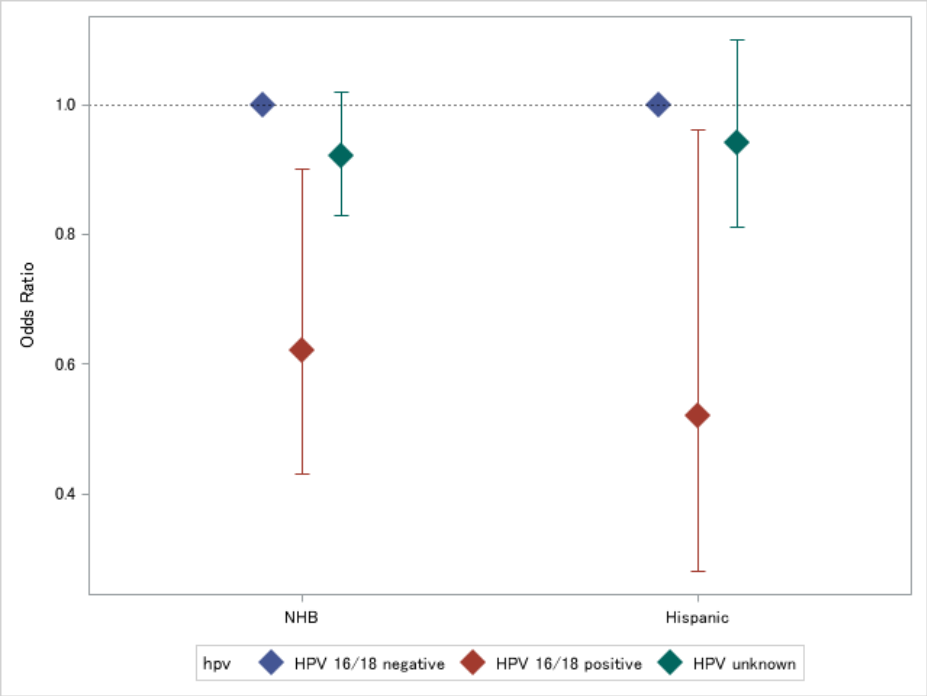


21a.



21b.

Appendix C (Continued)
Association of race/ethnicity with HPV status by site group - other than Oropharynx (Continued)

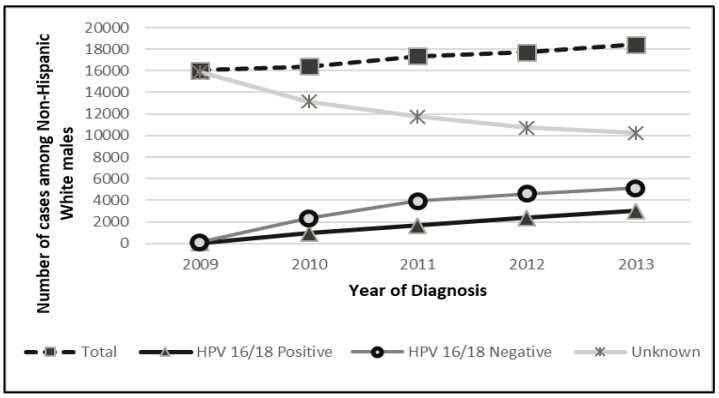


21c.

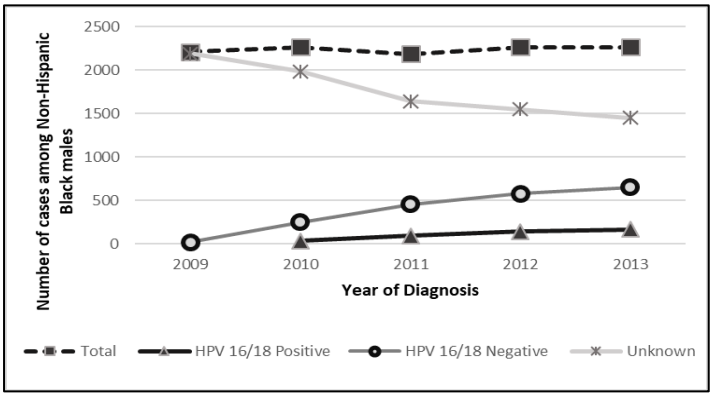
Appendix D
Temporal Trends by HPV status – all sites combined

Figure 22: Temporal trends by HPV status (for all HNSCC sites combined) among male HNSCC cases

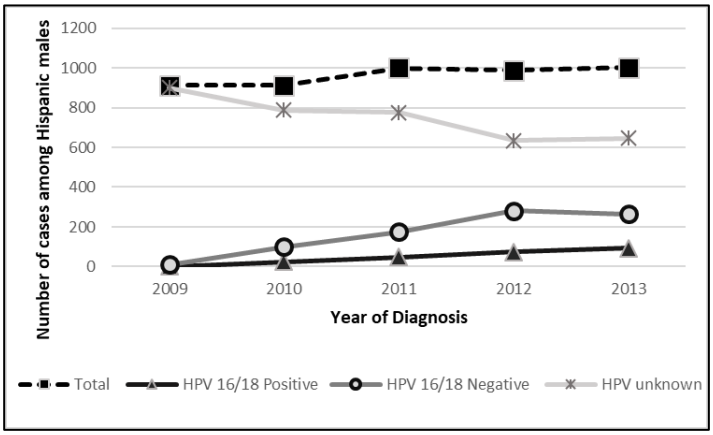
Appendix D (Continued)
Temporal Trends by HPV status – all sites combined (Continued)



22a. HNSCCs by HPV status (for all sites combined) among NHW males

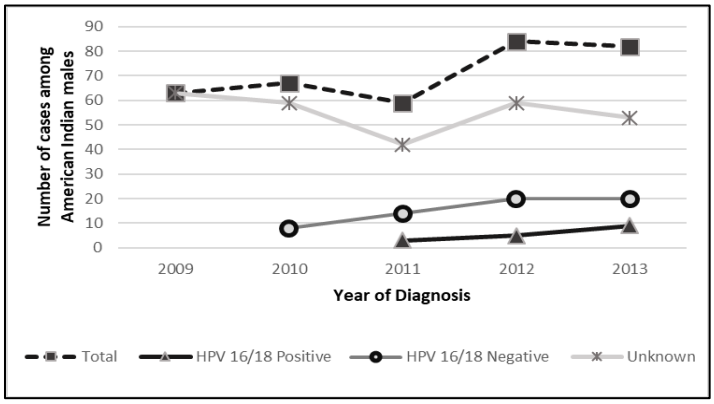


22b. HNSCCs by HPV status (for all sites combined) among NHB males

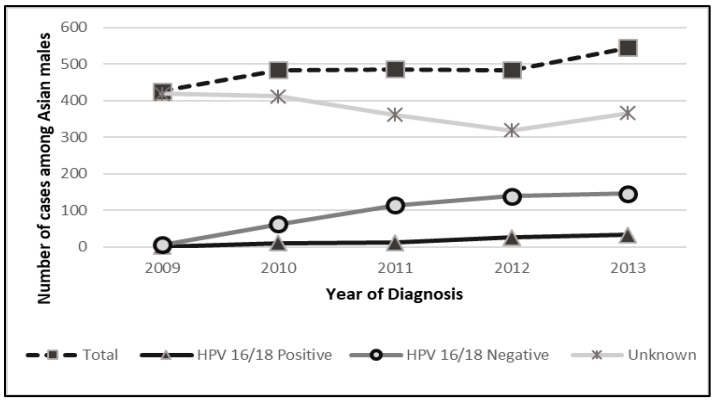


22c. HNSCCs by HPV status (for all sites combined) among Hispanic males

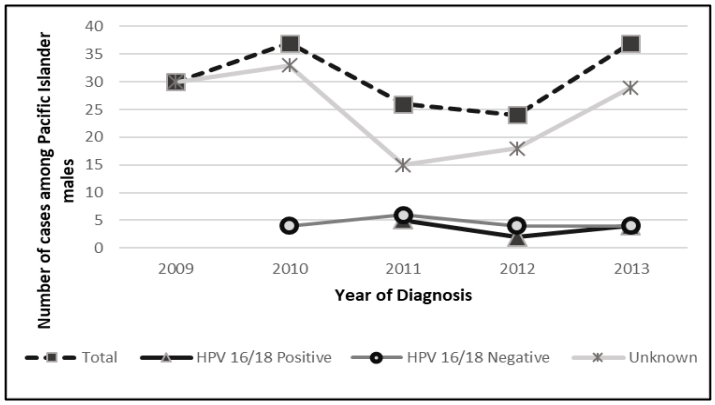
Appendix D (Continued)
Temporal Trends by HPV status – all sites combined (Continued)



22d. HNSCCs by HPV status (for all sites combined) among American Indian males



22e. HNSCCs by HPV status (for all sites combined) among Asian males



22f. HNSCCs by HPV status (for all sites combined) among Pacific Islander males

Appendix E
Racial/ethnic differences in HPV status – all sites combined

TABLE XVII
CRUDE AND ADJUSTED ASSOCIATION OF RACE/ETHNICITY WITH HPV STATUS AMONG HNSCC CASES (ALL SITES) USING NATIONAL CANCER DATABASE, 2009 - 2013.

	NHB vs. NHW OR (95% CI)	Hispanic[a] vs. NHW OR (95% CI)	American Indian vs. NHW OR (95% CI)	Asian vs. NHW OR (95% CI)	Pacific Islander vs. NHW OR (95% CI)
CRUDE					
HPV 16/18 negative[c]	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
HPV 16/18 positive[b]	**0.44 (0.40 – 0.49)**	**0.58 (0.50 – 0.67)**	**0.55 (0.32 – 0.94)**	**0.34 (0.27 – 0.44)**	1.23 (0.58 – 2.60)
HPV unknown[d]	**1.18 (1.12 – 1.25)**	**1.18 (1.09 – 1.27)**	1.16 (0.88 – 1.53)	1.05 (0.95 – 1.16)	**1.81 (1.10 – 2.97)**
ADJUSTED[h]					
HPV 16/18 negative[c]	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
HPV 16/18 positive[b]	**0.60 (0.53 – 0.67)**	**0.72 (0.62 – 0.84)**	0.61 (0.35 – 1.06)	**0.50 (0.39 – 0.64)**	1.59 (0.73 – 3.47)
HPV unknown[d]	1.03 (0.98 – 1.10)	1.08 (1.00 – 1.18)	1.13 (0.84 – 1.52)	1.06 (0.95 - 1.19)	**1.89 (1.12 – 3.20)**
ADJUSTED[i]					
HPV (all) negative[g]	1.00 (ref)	1.00 (ref)	--[j]	1.00 (ref)	--[j]
HPV 16/18 positive[b]	**0.51 (0.46 – 0.58)**	**0.66 (0.56 – 0.77)**		**0.44 (0.34 – 0.57)**	
HPV other HR positive[e]	**0.44 (0.35 – 0.56)**	**0.66 (0.49 – 0.88)**		**0.60 (0.39 – 0.93)**	
HPV LR positive[f]	**0.58 (0.50 – 0.69)**	**0.76 (0.61 – 0.94)**		**0.64 (0.46 – 0.88)**	
HPV unknown[d]	**0.93 (0.87 – 0.99)**	1.01 (0.92 – 1.10)		0.96 (0.85 - 1.08)	

[a] Includes Hispanic Whites and Blacks only.

[b] HPV 16/18 positive represents cases that were positive for HPV 16 or HPV 18 or both.

[c] HPV 16/18 negative represents cases that were negative for both HPV 16 and 18 but could be positive for HPV types other than 16/18 (includes "HPV negative for high-risk and low-risk types, HPV negative for high-risk types with no mention of low-risk types, Negative NOS", "HPV positive for low-risk types only", "HPV positive for specified high risk type(s) other than types 16 or 18", "HPV positive for high-risk type(s), NOS, high-risk type(s) not stated", HPV positive NOS risk and type(s) not stated") ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

[d] HPV unknown includes "Not applicable: Information not collected for this case", "Test ordered, results not in chart", "Test not done (test was not ordered and was not performed), including no pathologic specimen available for HPV testing", "Unknown or no information" ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

[e] HPV other High Risk+ includes HPV positive for High Risk types other than 16/18 or positive for high risk type NOS.

[f] HPV low risk+ includes HPV positive for low risk types only or HPV positive NOS.

[g] HPV (all) negative includes "negative for high-risk and low-risk type"s or "negative for high-risk types with no mention of low-risk type" or "HPV Negative, NOS" ("Oropharynx: CS Site-Specific Factor 10", 2013; NCI SEER Registrar Staging Assistant, n.d.).

[h] Adjusted for age at diagnosis, period of diagnosis, insurance status and area level income quartiles.

[i] Reran model (a) with five category HPV status as outcome.

[j] Sample was lower than 10 for some categories so these racial/ethnic groups were not included in this analysis.

Appendix F
Letter from UIC Institutional Review Board

Notice of Determination
Activity Does Not Represent Human Subjects Research

April 10, 2019

20190369-122497-1

Shaveta Khosla
Epidemiology and Biostatistics
Phone: (817) 703-1723

RE: **Protocol # 2019-0369**
"Assessment of Head and Neck Squamous Cell Carcinomas in Minority Racial/Ethnic groups in the US"

Funding Source/Sponsor: None

Dear Shaveta Khosla:

The UIC Office for the Protection of Research Subjects received your application, and has determined that this activity **DOES NOT meet the definition of human subject research** as defined by 45 CFR 46.102(e)/ 21 CFR 50.3(g) and 21 CFR 56.102(e).

Specifically, this study uses secondary de-identified data from the National Cancer Database.

You may conduct your activity without further submission to the IRB.

Please note:

- If this activity is used in conjunction with any other research involving human subjects, prospective IRB approval or a Claim of Exemption is required.
- If this activity is altered in such a manner that may result in the activity representing human subject research, a NEW Determination application must be submitted.

cc: Ronald C. Hershow
Caryn E. Peterson

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VITA

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Education

- **Master of Public Health**, Northern Illinois University, DeKalb, IL (August 2010)
- **Bachelor of Dental Surgery**, Baba Farid University, Punjab, India (July 2006)

Publications

- Brito MO, **Khosla S**, Santana L, Lubrano A, Martinez T, Eugeni A, Mehta SD, Novak RM. A community-based model of HIV care for men who have sex with men and transgender women in Chicago. International Journal of STD & AIDS; 31(2); 2020.

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- Brito MO, Lerebours L, Volquez C, Basora E, **Khosla S**, … Donastorg Y, Bailey RC. A clinical trial to introduce Voluntary Medical Male Circumcision for HIV prevention in areas of high prevalence in the Dominican Republic. PLoS One. 2015.

- Brito MO, Hodge D, Donastorg Y, **Khosla S**, Lerebours L, Pope Z. Risk behaviours and prevalence of sexually transmitted infections and HIV in a group of Dominican gay men, other men who have sex with men and transgender women. BMJ Open. 2015.

Posters and other scientific contributions

- Brito MO, **Khosla S**, Mehta SD, Novak RM. Virologic failure in HIV infected men who have sex with men and transgender women treated in a community based model vs. a hospital based model. IDWeek, October 2-6, 2019, Washington, DC. Abstract # 1307.

- **Khosla S**, Peterson CE. Head and Neck Cancer in South Asian Diaspora Living in the US, 2004 – 2013. Poster presented at CUGH 2019 - Annual Meeting of the Consortium of Universities for Global Health, Chicago, IL. March 8-10, 2019. Abstract # 1480.

- Pimentel R, Sullivan G, Perez M, **Khosla S**, Rondon JA, Mehta S, Brito MO. Long Term Neurocognitive Development of Children Born to Zika Infected Women in the Dominican Republic. Poster presented at CUGH 2019 - Annual Meeting of the Consortium of Universities for Global Health, Chicago, IL. March 8-10, 2019. Abstract # 847.

- Martinez B, Chimata R, Dedania N, **Khosla S**, Mayer S, Murthy V, Yeldandi V. The Acceptability and Impact of a Pilot Community Hands-Only Cardiopulmonary Resuscitation Training Program in India. Poster presented at Resuscitation Science Symposium. Chicago, IL. Nov 10-11, 2018. Abstract #227.

- Peña F, Pimentel R, **Khosla S**, Mehta S, Brito MO. Infant Microcephaly during the Zika Virus Epidemic in Dominican Republic, 2016-2017. Poster presented at Infectious Diseases Society of America. San Francisco, CA, USA. Oct 3-7, 2018. Abstract # 73462.

- Peña F, Pimentel R, **Khosla S**, Gilbert A, Perez CS, Mehta SD, Brito MO. Zika infection among pregnant women in the Dominican Republic, 2016-2017. Poster presented at CUGH 2018- Annual Meeting of the Consortium of Universities for Global Health, New York, NY. March 13-19, 2018. Abstract # 1560.

- Peña F, Pimentel R, **Khosla S**, Mehta S, Brito MO. Zika Virus Epidemic in the Dominican Republic, 2016. Open Forum Infectious Diseases. 4. S301-S301. 10.1093/ofid/ofx163.694. Poster presented at Infectious Diseases Society of America. San Diego, CA, USA. Oct 5, 2017.

- Brito MO, **Khosla S**, Lubrano A, Santana L, Davila J, Martinez T, Eugeni A, Novak, RM. A comparative analysis between a community-based and a hospital-based model of HIV care for men who have sex with men in the city of Chicago. Poster presented at the 9th IAS Conference on HIV Science. Paris, France. July 23-26, 2017. Abstract # 4518

- Mayer S, Fleming P, **Khosla S**, Lerebours L, Donastorg Y, Brito MO. Acceptability of Male Circumcision by Women Partners in a Clinical Trial in the Dominican Republic. Poster presented at the 9th IAS Conference on HIV Science. Paris, France. July 23-26, 2017. Abstract # A-854- 0229-02204

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- Gomez V, Feris-Iglesias J, Bernard R, Tran A, Bueno H, Crespo D, **Khosla S**…. Brito MO. An Outbreak of Chikungunya Fever among Employees of a Large Pediatric

Hospital in the Dominican Republic. Open Forum Infectious Diseases. 2016. Poster presented at Infectious Diseases Society of America. New Orleans, LA, USA. Oct 26-30, 2016.

- Peterson CE, **Khosla S**, Chen LF, Joslin CE, Davis FG. Racial differences in head and neck squamous cell carcinomas among cases identified through the National Cancer Database (1998-2012). Poster presented at American Public Health Association. Chicago, USA. 2015.

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- Pope Z, Hodge D, Donastorg Y, **Khosla S**, Lerebours L, Brito MO. Sexual risk behaviors and prevalence of sexually transmitted diseases in a cohort of Dominican men who have sex with men. Poster presented at 16th International Congress on Infectious Diseases. Cape Town, South Africa. April 2-5, 2014. Abstract#62.007

Teaching Experience

- **Lead Instructor** of Pre-Matriculation Program - Quantitative Methods Section at University of Illinois at Chicago (UIC), Chicago, IL (July 2019 to August 2019).
  Taught quantitative methods and epidemiologic concepts to incoming graduate students at UIC School of Public Health. Prepared the curriculum, designed pre-program knowledge assessment survey, created assignments and home-works, and lecture materials.

- **Adjunct Instructor** at Northern Illinois University, DeKalb, IL (Jan 2018 to May 2018)
  Taught undergraduate level Epidemiology course (PHHE 455: Public Health Epidemiology) to familiarize the undergraduate students with the principles and concepts of Epidemiology. Received positive feedback for the course with a high rating on the course evaluations.

- **Teaching Assistant** at UIC, Chicago, IL (Aug 2014 to Dec 2019). Courses taught included-
  - **Analytic and Research Methods in Public Health-** Assisted students in understanding the concepts; managed discussion board; graded assignments and exams.
  - **Epidemiologic Computing-** Assisted students during the lab sessions for a hands-on SAS course. Helped students with statistical programming and coding for data management and analysis. Conducted exam review sessions independently and proctored the exams.

- **Intermediate Epidemiologic Methods**- Assisted students in understanding intermediate epidemiologic methods coursework; graded the assignments and managed Blackboard.
- **Introduction to Epidemiology**- Answered student questions on Discussion Board and assisted students in understanding concepts for this completely online class. Graded the assignments, home-works and exams on Blackboard.

- **Speaker/Presenter** at College of Medicine, UIC (August 2013 to Dec 2019)
  - Conducted research didactics for residents. The content of didactics ranged from- introduction to statistical tests most used in research to an overview of epidemiologic study designs.
  - Arranged, conducted and supported small and large group Journal Clubs for residents/fellows.
  - Speaker at Noon Conferences – The content ranged from an overview of Epidemiology to the basics of Meta-analysis.

- **Teaching Assistant** at Northern Illinois University, DeKalb, IL (August 2008 to May 2010). Courses taught included-
  - **Public Health Epidemiology-** Assisted students in understanding the concepts of the course. Conducted one review session independently per semester, graded assignments, kept attendance record, proctored exams and maintained Blackboard.
  - **Ecology of Health**- Responsibilities included tutoring, grading, conducting discussion sessions, and maintaining student class record using CPS and Blackboard.
  - Also proctored and graded exams for other courses in the department.

- **Faculty** at TCY, India (January 2007 to June 2007)
  Counseled students; organized group discussion sessions and taught classes.

Research Experience

- **Research Assistant** at University of Illinois at Chicago College of Medicine (August 2013 to Dec 2019)
  My key role was to manage and analyze data from various national and international projects. The research projects focused on diverse areas ranging from Zika in pregnant women and infants in Dominican Republic to HIV care models in MSM populations in Chicago. Other responsibilities included- creating and maintaining RedCap databases, preparing questionnaires, designing research protocols, abstracting data from medical records, preparing IRB submissions, creating scientific posters and writing manuscripts.

- **Research Assistant** at University of Illinois at Chicago School of Public Health (February 2013 to August 2013)
  Prepared IRB documents for a study on Tuberculosis in Ukraine, and managed and analyzed the data. The data were later used to present the findings to a scientific delegation from Ukraine.

Other Work Experience

- **Intern** at Oak Crest DeKalb Area Retirement Center, DeKalb, IL (January 2010 to April 2010)
  Managed a program focused on dementia patients. Collected and compiled data from cognitive level screenings of residents with dementia. Identified residents with moderate dementia by assessing the cognitive ability of residents with Allen Cognitive Performance Modes and formed groups based on the cognitive level. Designed and implemented an activity for moderate dementia group. Assessed the progress of the program and reported results. Organized Pen Pal program for Oak Crest's independent residents where they write letters back and forth to elementary school students.

- **Intern** at BJS Dental College, Hospital and Research Institute, India (July 2005 to July 2006)
  Treated patients and organized health camps in schools and community centers.

Honors and Awards

- **Best Poster Award** at CCTS Translational Science Poster Competition, School of Public Health, University of Illinois at Chicago (2019)
- **Outstanding Graduate Student Award** from the Division of Research and Graduate Studies, Northern Illinois University (2010).
- UIC School of Public Health **Travel Award** (2019) and UIC Public Health Student Association **Travel Award** (2015), University of Illinois at Chicago.
- Nominated and elected as a member by the Alpha Eta Society.
