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Increasing Incidence of EBV-related Nasopharyngeal Carcinoma in the United States

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Running Title: SEER Data Suggests Increases in EBV-associated NPC

Precis: Using SEER data, we show that EBV-related non-keratinizing differentiated nasopharyngeal carcinoma (NPC) is starkly increasing across all genders and races. Furthermore, 32% of non-keratinizing NPC cases among African Americans occur under the age of 40, and this population exhibits the worse survival across all NPC subtypes.

Keywords: Nasopharyngeal Carcinoma, SEER, Incidence, Survival, Disparity, Epstein–Barr virus

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Abstract

Background: Incidence of nasopharyngeal carcinoma (NPC) has been historically low in the US. While etiological factors differ by histological subtype, Epstein-Barr virus (EBV) is accepted as the primary risk factor for non-keratinizing NPC. In light of the changing epidemiology of viral-associated cancers, it is important to evaluate temporal incidence of NPC in the US.
Methods: Incidence and survival data from 1973-2015 were obtained from the Surveillance, Epidemiology and End Results (SEER) Program. Stratified analyses were conducted to assess temporal trends in NPC by histological subtype, sex and race. The data were analyzed using SAS and Joinpoint Regression Software to determine age-adjusted incidence rates, trends in annual percent change (APC), and calculate 5-year relative survival estimates and Kaplan-Meier curves.
Results: Although overall NPC incidence is decreasing in the US, the non-keratinizing differentiated subtype is starkly increasing with an APC of approximately 4% among white males (95%CI: 2.5, 5.2), white females (95%CI: 1.9, 6.2), and black males (95%CI: 2.0, 5.7), 2.7% among black females (95%CI: 0.8, 4.6) and 1.8% among women of other race (95%CI: 0.4, 3.3). Racial disparities were noted, with 32% of non-keratinizing NPC cases among blacks occurred before the age of 40. Additionally, black males displayed consistently worse survival across all histological subtypes, while those individuals in the "other" race category, particularly females, experienced the highest 5-year relative survival estimates.
Conclusions: Our results indicate that the EBV-related differentiated NPC subtype is increasing across all genders and races in the US, with distinct incidence and survival disparities among blacks.

Introduction

Nasopharyngeal carcinoma (NPC) incidence varies greatly throughout the world. While historically rare in the United States, NPC is endemic to southeast China, Southeast Asia, the Middle East and North Africa [1]. Arising from the surface epithelium of the posterior nasopharynx [2], NPC is currently classified by the World Health Organization (WHO) into three major

histological subtypes: keratinizing squamous cell carcinoma (WHO type 1), non-keratinizing carcinoma (WHO type 2), which can further be divided into differentiated and undifferentiated, and basaloid squamous cell carcinoma (WHO type 3) [3]. These pathological classifications have been repeatedly correlated with clinicopathologic features, treatment response and prognosis [4, 5]. Basaloid squamous cell carcinoma is infrequent and thus is rarely reported in the literature [6]. Non-keratinizing NPC predominates in endemic regions, while the keratinizing subtype is most frequently observed in the non-endemic regions such as the United States (US) [7]. The unique geographic and ethnic distribution of NPC incidence throughout the world suggests a multifactorial etiology that involves viral, genetic and environmental components.

NPC incidence has been reported to rise monotonically with age in non-endemic countries, whereas in high-risk populations, such as southern China, incidence peaks between 45 and 54 years among both genders, implying that early exposure to carcinogens and Epstien-Barr virus (EBV) may result in younger onset NPC [8]. EBV, a herpesvirus most commonly known for causing mononucleosis, is generally accepted as the primary etiologic factor in non-keratinizing NPC. Increased latent EBV infection has been reported in dysplastic nasopharyngeal epithelium and NPC, suggesting that the infection occurs in the early stages of carcinogenesis [9-12]. Due to the ubiquitous nature of infection, and disproportionate global case distribution of NPC, several studies have assessed interactions between EBV and other lifestyle risk factors in high-risk populations. Dietary factors, namely early life exposure to Cantonese salted dried fish and other preserved foods containing volatile N-nitrosamines, have been implicated in NPC carcinogenesis through both the activation of latent EBV [13] and as independent carcinogens [14].

In non-endemic regions such as the United States, cigarette smoking and heavy alcohol consumption have been associated with keratinizing squamous cell carcinoma [15]. Compared to never smokers, heavy smokers have been reported to have a two- to four- fold increased risk of NPC [15-22]. Several studies have suggested that the effect conferred by smoking and alcohol primarily pertains to those diagnosed over age 50, suggesting a differing etiology among younger patients [15]. The increased prevalence of high-risk human papillomavirus (HPV) in oropharyngeal cancer etiology, paired with the similarities exhibited between the lymphoid and epithelium tissue of the oropharynx and nasopharynx, has led to investigation into the role of HPV in nasopharyngeal carcinogenesis. While results remain inconsistent, largely due to small sample sizes, there is evidence to suggest the role of HPV, and even HPV/EBV coinfection, in NPC [4, 23-26].

It is important to evaluate incidence of NPC in the US over time in light of the changing epidemiology of HPV-associated oral cancers. Thus, in these analyses, we assess NPC incidence and mortality trends in the United States from 1973-2015 using the Surveillance, Epidemiology and End Results Program (SEER). In doing so, we aim to identify potential variation across race and sex and draw on the literature to make inferences on changing etiology over time.

Methods

Data Selection and Criteria

Cancer incidence and survival data were obtained from the Surveillance, Epidemiology and End Results (SEER) Program. For this analysis, SEER 9 data were used, which includes data from the following registries; Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound and Utah registries. Data from 1973-2015 were available

for all sites, with the exception of Seattle-Puget Sound and Atlanta, which joined in 1974 and 1975, respectively. Corresponding population estimates were obtained from SEER*Stat 8.3.5 [27] which are based upon the US Census Bureau's Population Estimates Program [28]. In addition to diagnosis, case information included: age, sex, race, date of diagnosis, SEER historical staging, histology, cause of death classification, and survival time in months. Due to the small sample size of American Indians/Alaska Natives, this race group was combined with Asian/Pacific Islander to create the 'Other' race grouping.

Tumor site and histology were identified according to the International Classification of Diseases for Oncology (ICD-O-3) [6, 29]. Histologic subtypes for NPC (Site codes: C11.0-C11.9) included: keratinizing squamous cell carcinoma (ICD-O histology codes 8070 and 8071), differentiated non-keratinizing carcinoma (ICD-O histology codes 8072 and 8073), undifferentiated non-keratinizing carcinoma (ICD-O histology codes 8020, 8021, and 8082) and 'carcinoma not otherwise specified' (ICD-O histology code 8010) [5]. In accordance with WHO guidelines, differentiated and undifferentiated non-keratinizing carcinomas were analyzed both separately and jointly to comprise the single non-keratinizing group. Overall NPC was defined as the culmination of all the aforementioned histological groupings. Basaloid squamous cell carcinomas (ICD-O histology code 8083) were excluded from these analyses due to small sample size (N=30). Additional exclusion criteria included unknown race, non-malignant carcinoma, and prior diagnosis of malignancy. Patient characteristics were assessed by histological subgrouping and further evaluation of age at diagnosis (in five year groupings) was conducted by visually displaying case frequencies by race for overall, keratinizing and non-keratinizing NPC.

Sex stratified exploratory analyses assessing incidence trends in extranodal NK/T-cell lymphoma, nasal type (ICD-O histology code 9719) were conducted for all effective years, 2001-2015, to further evaluate the potential role of EBV in US malignancies.

Incidence Trends

Age-adjusted incidence rates (standardized to the US population) and annual percent change (APC) were assessed using a log-linear model stratified by race, sex, and histological classification in Joinpoint Regression Program version 4.5.0.1 [30]. Joinpoint utilizes a Monte Carlo permutation method in order to assess number of joinpoints, slope in the trends, as well as their corresponding significance [31]. In circumstances where no cases were reported within a given year, a half-case was added to the age strata with the largest population to enable computation on the log-linear scale [31, 32]. SAS 9.4 software [27] was used to shape the data and generate descriptive statistics.

Survival Analysis

Individual-level data from the SEER*Stat case listing session was used to create Kaplan Meier curves in SAS 9.4 software. Graphs were gender specific, stratified by histologic type, and strata were compared using log-rank tests. Patients whose survival data were obtained from death certificates or autopsy only, as well as those with unknown survival duration, were excluded. In addition, those who cases with unknown age or those with a previous invasive cancer diagnosis were excluded from survival analyses. Five year relative survival, calculated as the ratio of the observed survival for NPC patients to the expected survival rate based on age, race, and calendar year, were computed using the Kaplan-Meier method in SEER*Stat. Expected survival life tables were constructed using the US Decennial Life Tables from the National Center for Health Statistics (NCHS) and from the US Annual Life Tables from NCHS for the years 2001–2014 [27].

Results

Between 1973 and 2015, 4,447 cases of NPC were reported among males and 1,838 among females in the US. Regardless of histological subtype, males accounted for ~70% of the overall cancer burden. In general, the peak incidence occurred at age 55 for both sexes, with the undifferentiated non-keratinizing carcinoma subgroup representing the youngest mean age at diagnosis (49.34 and 49.15 for males and females, respectively). Expository analyses revealed a bimodal distribution among blacks, with 25% of all cases being diagnosed under the age of 40, as compared to 12% and 21% of their white and other counterparts, respectively. While this trend was not apparent for keratinizing NPC, 32% of non-keratinizing NPC cases among blacks, 21% among whites and 22% among the other race group occurred under the age of 40 (Supplementary Figure 2). The keratinizing squamous cell carcinoma subtype made up the majority of NPC cases, largely due to its predominance among white patients, who accounted for 49% of the overall sample size. Non-keratinizing NPC was diagnosed more frequently among blacks and predominated among the other race group. Among those with non-keratinizing NPC, the undifferentiated cell type was more frequently reported across all races. SEER summary stage was available for cases diagnosed prior to 2004, and most cases were diagnosed with regional disease (Table 1).

While NPC incidence rates for the overall population appeared to have remained relatively stagnant among males (APC: -0.2 [95%CI: -0.4, 0.1]) and females (APC: -0.4 [95%CI: -0.8, 0.0]), these trends vary greatly across both race and histology. At the beginning of the study period, the expected age standardized rate (EASR) for white and black males were 0.67 and 0.66 per 100,000, respectively. White and black females both had notably lower rates, with EASRs of 0.34 and 0.16 per 100,000, respectively. The other race category, largely comprised of Asian/Pacific Islanders,

exhibited the highest NPC rates, with an EASR of 4.79 and 1.76 per 100,000 among males and females, respectively. Temporal assessment of NPC incidence revealed significant decreases in white males (APC: -1.2 [95%CI: -1.5, -0.8]) and females (APC: -1.6 [95%CI: -2.1, -1.0]), black females (APC: -1.4 [95% CI: -2.5, -0.4]) as well as other males (APC: -1.0 [95%CI: -1.4, -0.6]) and females (APC: -1.3 [95%CI: -1.9, -0.7]) (Table 2).

These observed decreases in overall NPC are largely attributable to declines in the predominant keratinizing squamous cell carcinoma subtype. Joinpoint regression results for the overall population exhibited non-significant increases in keratinizing carcinoma among men from 1973-1985 (APC: 1.1 [95%CI: -1.2, 3.5]), followed by a significant decrease from 1985-2015 (APC: -2.6 [95%CI: -3.2, -2.1]); similar declines were observed among women (APC: -2.4 [95%CI: -3.0, -1.7]). While this pattern of reduced keratinizing NPC is seen across all races, it was not found to be significant among black males, and demonstrated the greatest impact among males (APC: -3.4 [95%CI: -4.1, -2.7]) and females (APC: -4.2 [95%CI: -5.1, -3.2]) of the other race category (Table 2).

Non-keratinizing NPC revealed two very different patterns in incidence trends, depending on histological subtype. Undifferentiated carcinomas significantly decreased with an APC of approximately -2% among white males (95%CI: -2.8, -1.3) and females and (95%CI: -3.0, -0.6), -2.7% among black females (95%CI: -4.2, -1.1), -1.5% among other males (95%CI: -2.2, -0.6) and -2.4% among women of other race (95%CI: -3.5, -1.4). The differentiated subtype, on the other hand, increased starkly in incidence with an APC of approximately 4% among white males (95%CI: 2.5, 5.2), white females (95%CI: 1.9, 6.2), and black males (95%CI: 2.0, 5.7), 2.7%

among black females (95%CI: 0.8, 4.6) and 1.8% among women of other race (95%CI: 0.4, 3.3). This dichotomy in incidence between differentiated and undifferentiated led to an attenuation in the overall trends of non-keratinizing NPC (Table 2).

Exploratory analyses on incidence trends in extranodal NK/T-cell lymphoma nasal type revealed very similar trends to those apparent in differentiated non-keratinizing NPC. Between 2001 and 2015, incidence increased among both sexes, with an APC of 3.2% (95%CI: 0.7, 5.8) among males and 3.9% (95%CI: 0.2, 7.8) among females. Race stratified analysis demonstrated even steeper increases among white males (APC: 3.8 [95%CI: 0.6, 7.1]) and females (APC: 4.1 [95%CI: 0.7, 7.6]). No significant increases were notes for the other race groups, likely due to small sample sized within these groups.

5-year relative survival estimated by race, sex and histological subtype can be found in Table 3. For all NPC types, 5 year relative survival was 53.0% among males, and 55.8% among females. Figure 1 displays sex stratified Kaplan Meier survival plots by histological subgrouping. Both male and female patients with keratinizing squamous cell carcinoma had the worst survival when compared to the other histological subtypes (log rank $p<0.001$). 5-year relative survival rates for keratinizing squamous cell carcinoma were 41.9% and 41.5% for males and females of all races, respectively. While black males had consistently poorer survival across all histological subtypes, those individuals in the "other" race category, particularly females, experienced the highest 5-year relative survival estimates (Table 3).

Discussion

This is the first study, to our knowledge, to assess temporal changes in NPC incidence in the

United States. Although overall NPC incidence appears to be decreasing in the US, the EBV-related differentiated non-keratinizing NPC subtype is increasing at a concerning rate among all race groups and genders in the US. NPC has long been considered a relatively rare disease in the US, with a reported incidence rate less than 1 per 100,000 [2, 33, 34]. Nevertheless, in endemic regions, NPC remains a major public health problem, with annual incidence rates exceeding 20 per 100,000 individuals [33]. Several studies have previously reported decreased incidence of NPC in successive generations of Chinese migrants to the US [35]; however, the EASR among those belonging to the other race category, of which 98% identify as Asian/Pacific Islanders, remain over 5 times higher in females and 7 times higher among males, when compared to their white counterparts. Additionally, the rate of change in overall NPC incidence, represented as APC, between the white and other race individuals remained comparable throughout the study period, leading to continued disparity among this race group across time.

EBV, a prominent etiological factor in NPC, is a ubiquitous virus that infects and persists latently in over 90% of the global population [36]. Although primary infection is often subclinical, EBV replication can occur in oropharyngeal epithelial cells [37] as well as B lymphocytes in normal and malignant nasopharyngeal tissue [38]. EBV-encoded RNA has repeatedly been detected in both premalignant and malignant tissues of primarily non-keratinizing NPC[39-41]; nevertheless, few studies, particularly in non-endemic countries, have characterized the potential differences in etiology between differentiated and undifferentiated NPC. Antibody titers, particularly for IgA, have also been shown to not only precede cancer development [42], but to be associated with prognosis and recurrence [43]. A considerable amount of research has been conducted in order to determine whether particular strains of EBV may, at least in part, explain the international patterns

of NPC [44-47]. Several different sequence variations have been detected in the oncogenic viral latent membrane protein 1 (LMP1) of EBV in NPC tumors [44, 48-50], however, there remains no strong evidence to suggest an increased risk associated with different EBV variants [33, 49-52]. In this study, we found differentiated non-keratinizing NPC incidence to be increasing among all sex and race groups, leading to speculation of an increased role of EBV in US NPC. Exploratory analyses into SEER incidence trends of extranodal NK/T-cell lymphoma, a form of non-Hodgkin's lymphoma consistently associated with EBV [53-67], demonstrated significant increases in this cancer type among both genders over this time period, further supporting the possibility for an increasing role in EBV etiology in US malignancies (Supplemental Figure 1).

In certain endemic populations, such as the Cantonese, early age incidence peaks in NPC are generally associated with childhood consumption of, or even traditional weaning by [68], salted fish and other preserved foods high in volatile N-nitrosamines [13]. Early-life infection by EBV [69, 70], as well as genetic predisposition, have both been proposed as possible risk factors for early onset NPC, but little consensus has been reached regarding the etiology of such cases in the US. Although the average age at diagnosis in our study was 55 among both sexes, we noted a bimodal distribution in cases among blacks, with 25% of patients being diagnosed under the age of 40 as compared to 12% of their white counterparts. While this distribution has been observed previously [35], we noted this disparity to be particularly apparent in the non-keratinizing subtype, where 32% of cases among blacks occurred before the age of 40 (Supplemental Figure 2). Though we are unable to definitively conclude that the increase in these young onset cases is due to EBV alone, EBV seroprevalence has been reported to be significantly higher among African-American youth when compared to their white peers [71, 72]. Further studies are needed in order to properly assess the

role childhood infection by EBV, as well as possible gene-environment interactions in the US population.

The majority of case control studies report a 2- to 4-fold increased risk in NPC among smokers [15, 16, 18-22]. Vaughan et al. estimated that two thirds of keratinizing NPC in the US are attributable to smoking, while both subtypes of non-keratinizing carcinoma failed to demonstrate significant associations [15]. Decreases in smoking prevalence in the US [73] may explain the decreases in keratinizing squamous cell carcinoma seen in our analyses. Diet, which has been the primary nonviral exposure associated with NPC in endemic regions, has been postulated to impact NPC primarily thought the consumption of preformed nitrosamines or nitrosamine precursors [74]. While cultural differences in dietary patterns preclude early and repeated exposure to salted fish [75], harissa, quaddid and touklia [76] from US dietary etiology, preserved meats, which contain high levels of added nitrites, have been studied and found not to be significantly associated with NPC carcinogenesis [74]. Although this particular study did not assess genetic variation, individuals processing the c2/c2 metabolic genotype for CYP2E1, a catalytic enzyme for the metabolic activation of low-molecular weight nitrosamines, have been shown to experience a 2.6-fold increased risk of NPC when compared to those possessing one or two copies of the wild-type allele [77]. Moreover, alcohol, in addition to its innate role as a carcinogen [15, 18], has been shown in animal models to increase the carcinogenicity of ingested nitrosamines [78, 79], further stressing the importance of dietary interaction studies in the understanding of nasopharyngeal carcinogenesis.

Our study confirmed previous reports of a survival advantage of the undifferentiated non-keratinizing morphology over the differentiated non-keratinizing and keratinizing squamous

cell NPC [5, 35]. Additionally, we found that the 'other' racial grouping had consistently improved survival when compared to white and black patients, particularly among those presenting with keratinizing squamous cell carcinoma; these findings are consistent with other reports of a survival advantage among Chinese/Asian patients [5, 35, 80]. One proposed rationale for this observation may be the high proportion of polymorphisms in the epidermal growth factor receptor (EGFR) found in the Chinese/Asian population, leading to lower EGFR expression, and consequently improved prognosis [5, 81-84].

There are several limitations present in this study. Although the use of SEER-9 allows for temporal analysis of cancer trends since 1973, it represents only half of the participating registries to date. Additionally, population estimates used for trends analyses were only available for the White, Black and Other race categories until 1990, resulting in our inability to assess age-adjusted NPC incidence trends in specific other races (American Indian/Alaska Native and Asian/Pacific Islander) or by Hispanic ethnicity for the entire study period. Treatment variables, particularly those pertinent to NPC such as chemotherapy and radiation, are not suggested for use by SEER due known data gaps for these variables. The absence of data regarding comorbidities, smoking, drinking behavior, and EBV prevalence, limits our ability to make definitive statements regarding the underlying etiology influencing the observed trends. Although more precise treatment and comorbidity variables are available by linking the SEER database to the Medicare claims database, the majority of NPC patients in this study are too young to qualify for Medicare (<65 years old). Trends in adenocarcinoma of the nasopharynx, largely associated with occupational exposures such as wood dust [85-87], were not able to be assessed due to small sample sizes. Finally, the WHO classification system for NPC had changed several times throughout the study period,

consequently leading to concerns regarding the interpretability of subtype specific results. That being said, the changes within the WHO guidelines were made in the grouping of the subtypes, not the pathology; this study utilizes morphology codes to define NPC subtypes, and therefore the changes in WHO classifications have no effect on the study nor the conclusions.

Although NPC remains relatively rare in the overall US population, the EBV-related differentiated subtype is increasing across all genders and races. Many studies assessing non-keratinizing NPC, particularly in the US, aggregate differentiated and undifferentiated carcinoma due to lack of sample size; the results of this study highlight the need for additional research to elucidate the potential etiological differences between these histological subgroups, consequently addressing the rationale for the disparity in the observed incidence trends. Due to the fact that prospective cohort studies with comprehensive exposure assessment would require decades to recruit a sufficient sample size to assess gene-environment interactions, multicenter studies or case-control studies in high incidence regions may prove to be a more feasible method to improve understanding of NPC etiology. Additionally, studies evaluating the biological mechanism by which EBV is involved in NPC are needed in order to move EBV preventative and targeted therapeutic methods forward, such as immunotherapy or even an EBV vaccine. Recent interest into the possible role of HPV in NPC, likely representing subepithelial extension from the oropharynx due to the lack of anatomical constraints in Waldeyer's ring [1], may also aid in understanding incidence trends and NPC pathogenesis. Finally, comprehensive characterization of risk factors among young adults is needed in order to reveal the cause for the adolescent incidence peak observed in African American populations in this study.

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Figure Legends
Figure 1: Kaplan Meier Survival Curves for Overall Survival by Sex and Histology

Table 1: Nasopharyngeal Carcinoma Distribution, 1973-2015, by Sex and Histology

	Overall Nasopharyngeal Carcinoma		Keratinizing Squamous Cell Carcinoma		Differentiated Non-Keratinizing Carcinoma		Undifferentiated Non-Keratinizing Carcinoma		Carcinoma NOS	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Number of Cases, N (%)	4447 (70.76)	1838 (29.24)	1979 (70.30)	836 (29.70)	710 (73.35)	258 (26.65)	996 (70.49)	417 (29.51)	762 (69.97)	327 (30.03)
Mean age (SD)	54.55 (15.00)	55.36 (16.47)	57.35 (13.65)	59.24 (14.76)	53.91 (13.24)	54.18 (16.30)	49.34 (16.28)	49.15 (16.45)	54.69 (16.22)	54.31 (18.02)
Race										
White	2175 (48.91)	893 (48.59)	1247 (63.01)	568 (67.94)	268 (37.75)	68 (26.36)	361 (36.24)	143 (34.29)	299 (39.24)	114 (34.86)
Black	426 (9.58)	163 (8.87)	209 (10.56)	69 (8.25)	60 (8.45)	28 (10.85)	85 (8.53)	41 (9.83)	72 (9.45)	25 (7.65)
Asian/Pacific Islander	1813 (40.77)	761 (41.40)	510 (25.77)	194 (23.21)	377 (53.10)	156 (60.47)	543 (54.52)	227 (54.44)	383 (50.26)	184 (56.27)
American Indian/Alaska Native	33 (0.74)	21 (1.14)	13 (0.66)	5 (0.60)	5 (0.70)	6 (2.33)	7 (0.70)	6 (1.44)	8 (1.05)	4 (1.22)
Stage										
Localized	388 (8.72)	175 (9.52)	202 (10.21)	103 (12.32)	47 (6.62)	12 (4.65)	91 (9.14)	43 (10.31)	48 (6.30)	17 (5.20)
Regional	1786 (40.16)	759 (41.29)	848 (42.85)	366 (43.78)	235 (33.10)	90 (34.88)	441 (44.28)	180 (43.17)	262 (34.38)	123 (37.61)
Distant	493 (11.09)	190 (10.34)	281 (14.20)	102 (12.20)	54 (7.61)	10 (3.88)	100 (10.04)	52 (12.47)	58 (7.61)	26 (7.95)
Unstaged	247 (5.55)	132 (7.18)	122 (6.16)	75 (8.97)	11 (1.55)	4 (1.55)	47 (4.72)	19 (4.56)	67 (8.79)	34 (10.40)
Cases diagnosed 2004+	1533 (34.47)	582 (31.66)	526 (26.58)	190 (22.73)	363 (51.13)	142 (55.04)	317 (31.83)	123 (29.50)	327 (42.91)	127 (38.84)

	All		White		Black		Other	
	Male	Female	Male	Female	Male	Female	Male	Female
Overall Nasopharyngeal	-0.2 (-0.4, 0.1)	-0.4 (-0.8, 0.0)	-1.2* (-1.5, -0.8)	-1.6* (-2.1, -1.0)	-0.1 (-1.0, 0.7)	-1.4* (-2.5, -0.4)	-1.0* (-1.4, -0.6)	-1.3* (-1.9, -0.7)
Keratinizing	1.1 (-1.2, 3.5)ɣ -2.6* (-3.2, -2.1)¥	-2.4* (-3.0, -1.7)	-2.1* (-2.6, -1.6)	-2.4* (-3.2, -1.6)	-1.2 (-2.4, 0.0)	-2.3* (-4.1, -0.4)	-3.4* (-4.1, -2.7)	-4.2* (-5.1, -3.2)
Non-Keratinizing	1.0* (0.5, 1.5)	1.2* (0.5, 1.8)	0.5 (-0.2, 1.1)	-0.0 (-1.1, 1.1)	0.6 (-0.8, 2.0)	-0.6 (-2.1, 0.9)	-0.8* (-1.5, -0.2)	-0.6 (-1.5, 0.2)
Differentiated	3.0* (2.1, 3.9)	4.4* (3.0, 5.9)	3.8* (2.5, 5.2)	4.0* (1.9, 6.2)	3.9* (2.0, 5.7)	2.7* (0.8, 4.6)	-0.1 (-1.3, 1.0)	1.8* (0.4, 3.3)
Undifferentiated	-0.5 (-1.1, 0.1)	-0.8* (-1.5, -0.0)	-2.1* (-2.8, -1.3)	-1.8* (-3.0, -0.6)	-1.6 (-3.3, 0.2)	-2.7* (-4.2, -1.1)	-1.5* (-2.2, -0.6)	-2.4* (-3.5, -1.4)

*** denote statistical significance at α=0.05**

ɣ 1973-1985

¥ 1985-2015

Table 3: Five-year Relative Survival Estimates by Sex and Race [% (CI)]

	All		White		Black		Other	
	Male	Female	Male	Female	Male	Female	Male	Female
Cell Type, % (CI)								
Overall Nasopharyngeal	53.0 (51.3, 54.7)	55.8 (53.2, 58.4)	47.7 (45.2, 50.2)	45.7 (41.8, 49.6)	44.4 (38.7, 49.9)	56.5 (47.1, 64.8)	60.8 (58.2, 63.2)	66.1 (62.2, 69.7)
Keratinizing	41.9 (39.4, 44.4)	41.5 (37.6, 45.4)	37.7 (34.6, 40.9)	37.1 (32.3, 41.8)	35.5 (27.7, 43.4)	35.9 (22.9, 49.0)	53.2 (48.3, 57.7)	54.3 (46.3, 61.6)
Non- Keratinizing	64.7 (62.0, 67.2)	67.7 (63.5, 71.6)	64.4 (59.8, 68.6)	61.0 (52.7, 68.3)	54.4 (44.4, 63.3)	70.6 (55.8, 81.2)	66.4 (62.8, 69.7)	70.5 (65.1, 75.2)
Differentiated	63.1 (58.7, 67.1)	63.4 (56.0, 69.9)	62.3 (55.0, 68.7)	51.6 (36.2, 65.0)	49.5 (32.8, 64.2)	66.5 (41.2, 82.9)	65.3 (59.4, 70.5)	67.3 (58.1, 74.9)
Undifferentiated	65.8 (62.4, 69.0)	70.1 (64.8, 74.8)	65.8 (59.7, 71.1)	65.0 (55.1, 73.3)	57.1 (44.5, 67.9)	72.6 (53.2, 85.0)	67.1 (62.5, 71.3)	72.5 (65.6, 78.3)
NOS	54.6 (50.4, 58.6)	66.2 (59.7, 71.9)	51.9 (45.0, 58.4)	58.6 (46.5, 68.9)	47.7 (34.3, 59.9)	69.1 (42.9, 85.1)	57.5 (51.8, 62.9)	69.9 (61.6, 76.7)

Figure 1: Kaplan Meier Survival Curves for Overall Survival by Sex and Histology