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Racial and ethnic disparities in nasopharyngeal cancer with an emphasis among Asian Americans

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Abstract

Despite the overall decreasing incidence, nasopharyngeal cancer (NPC) continues to cause a significant health burden among Asian Americans (AAs), who are a fast-growing but understudied heterogeneous racial group in the United States. We aimed to examine the racial/ethnic disparities in NPC incidence, treatment, and mortality with a specific focus on AA subgroups. NPC patients aged ≥15 years were obtained from the Surveillance, Epidemiology, and End Results (SEER) 18 (1975-2018). AAs were divided into Chinese, Filipino, Vietnamese, Hawaiian, Japanese, Laotian, Korean, Cambodian, Indian/Pakistani and other Asian/Pacific Islanders (APIs). Age-adjusted incidence was calculated using the SEER*Stat software. Cox proportional and Fine-Gray subdistribution hazard models were used to calculate overall and cause-specific mortalities after adjusting for confounders. Among the total 11 964 NPC cases, 18.4% were Chinese, 7.7% Filipino, 5.0% Vietnamese, 1.2% Hawaiian, 1.0% Japanese, 0.8% Laotian, 0.8% Korean, 0.6% Cambodian, 0.5% Indian/Pakistani and 4.4% other APIs. Laotians had the highest age-adjusted NPC incidence (9.21 per 100 000), which was 18.04 times higher than it in non-Hispanic Whites (NHWs). Chinese and Filipinos observed lower overall mortalities, however, Chinese saw increased NPC-specific mortality than NHWs. Disparities in mortality were also found across different histology subtypes. This is the first and largest study examining the NPC incidence and outcomes in AA subgroups. The significant disparities of NPC within AAs underline the importance of adequate AA-subgroup sample size in future studies to understand the prognostic role of ethnicity in NPC and advocate more ethnically and culturally tailored cancer prevention and care delivery.

KEYWORDS
Asian Americans, incidence, mortality, nasopharyngeal cancer, racial/ethnic disparities

What's new?

Nasopharyngeal cancer is a considerable health concern for Asian Americans, for reasons that remain unclear. In this population-based study, disparities in various features of nasopharyngeal cancer, including incidence, treatment, and mortality, were examined among different Asian

Abbreviations: AA(s), Asian American(s); AAIR, age-adjusted incidence rate; APC, annual percentage change; APIs, Asian/Pacific Islanders; CI, confidence interval; CVD, cardiovascular disease; DNKC, differentiated nonkeratinizing carcinoma; HR, hazard ratio; ICD, International Classification of Diseases for Oncology; IRR, incidence rate ratio; KSCC, keratinizing squamous cell carcinoma; NHB, non-Hispanic Black; NHW, non-Hispanic White; NPC, nasopharyngeal cancer; REF, reference; RT, radiation therapy; SEER, Surveillance, Epidemiology and End Results; UNKC, undifferentiated nonkeratinizing carcinoma; US, United States.

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American ethnic subgroups. Significant disparities in incidence, tumor stage and grade, histology, treatment, and survival outcome were observed between Asian Americans and other racial groups, as well as within Asian American subgroups. Incidence was notably high among Laotians, while overall mortality was declining among Chinese and Filipinos. The results emphasize the importance of investigating and understanding the role of ethnicity in nasopharyngeal cancer.

1 | INTRODUCTION

Nasopharyngeal cancer (NPC) is characterized by its distinct geographic distribution and risk factors, with the highest incidence in Southeastern Asia and Southern China.[1] Although the incidence of NPC is lower in the United States compared to endemic regions, NPC causes a significant health burden among Asian Americans (AAs).[2]

AAs are defined as individuals with origins in any of the original peoples of the Far East, Southeast Asia or the Indian subcontinent.[3] AAs are the fastest growing racial group in the United States, with the population nearly doubled between 2000 and 2019 from 11.9 million to 22.4 million.[4] By 2060, the population of AA is predicted to surpass 46 billion.[4] In 2019, Chinese Americans were the largest group, accounting for 24% of the AAs, followed by Indians (21%), Filipinos (19%), Vietnamese (10%), Koreans (9%), Japanese (7%) and others (15%).[4]

AAs have historically been studied in aggregate and separate national-level epidemiological information on NPC remains unavailable. McCracken et al observed significant disparities in the incidence, risk factor and screening of prostate, breast, lung, colon/rectum, stomach, liver and cervix cancer in five AA subgroups in California including Chinese, Filipino, Vietnamese, Korean and Japanese.[5] Notably their study did not include NPC as a cancer site. Several prior studies have used the Surveillance, Epidemiology and End Results (SEER) data to examine the racial and ethnic disparities in NPC,[6-16] either combining AA subgroups as one single group or with limited subgroup categorization.[6-12,14-16] Dodge et al examined the disparities of NPC between California Hmong (an ethnic group from Southern China and Southeast Asia), Asian/Pacific Islanders (APIs) and non-Hispanic White (NHW) using the California Cancer Registry data from 1988 to 2000.[17] They found that the NPC mortality of Hmong was 52 and 6 times greater than HNW and APIs, respectively. Hmong were also more likely to be diagnosed at metastatic stage and less likely to receive treatment.[17] Therefore, there is evidence that substantial disparities exist within the AA population that have not been characterized in a systemic way.

AAs comprise of a diverse population with unique genetic factors, socioeconomic status, immigration history, cultural background, religious practices, health behaviors and health care access. The paucity of subgroup-specific information limits targeted cancer prevention and management in AAs.[4] Hence, we aim to examine the NPC incidence and mortality by disaggregating AAs into 10 subgroups, which is the most diversified breakdown of AAs so far.

2 | METHODS

2.1 | Study population

SEER 18 program collects cancer incidence data from 18 population-based cancer registries and covers approximately 28% of the US population with estimated case ascertainment around 98%.[18] Patients who were 15 years old or above with a diagnosis of NPC as "one primary only" or "first of 2 or more primaries" between 1975 and 2018 were extracted (Figure S1). The WHO International Classification of Diseases for Oncology (ICD-O-3 code) C11.0 to C11.9 were used to select NPC patients. AA subgroups with NPC cases ≤ 50 were combined into a single group—"other APIs" to allow for statistically meaningful analyses (Table S1). Race/ethnicity was categorized into NHW, non-Hispanic Black (NHB), Hispanic, Chinese, Filipino, Vietnamese, Hawaiian, Japanese, Laotian, Korean, Cambodian, Indian/Pakistani and other APIs. Age at diagnosis (15-39, 40-49, 50-59, 60-69 and 70+ years), sex (female vs male), marital status at diagnosis (married vs unmarried) and year of diagnosis (1975-1985, 1986-1995, 1996-2005 and 2006-2018) were also obtained. NPC histology was classified as keratinizing squamous cell carcinoma (KSCC) (ICD-O codes 8070 and 8071), differentiated non-keratinizing squamous cell carcinoma (DNKC) (ICD-O codes 8072 and 8073), undifferentiated non-keratinizing squamous cell carcinoma (UNKC) (ICD-O codes 8020, 8021, 8082 and 8010 [carcinoma, not other specified]) and others.[14,15] Besides, information regarding stage (localized, regional and distant), grade (grade I: "well differentiated," grade II: "moderately differentiated," grade III: "poorly differentiated" and grade IV: "undifferentiated or anaplastic"), radiation therapy (RT), chemotherapy and surgery were also extracted. The SEER "Historic Stage" and "Combined Summary Stage" variables were used to define the stage at diagnosis. For RT, no/unknown was defined as "none/unknown, refused (1988+) or recommended, unknown if administered." Chemotherapy was coded as "yes vs no/unknown" in the SEER*Stat software (version 8.3.9).[19] The SEER Historical Staging and Coding Manuals were used to code surgery (yes vs no).[20]

2.2 | Statistical Analysis

SEER 9, plus the remainder of California and New Jersey, November 2016 Submission (1990-2014) with detailed API plus NHW was used to calculate age-adjusted incidence rate (AAIR) and incidence rate ratio (IRR) using the SEER*Stat software and US 2000 Census data for

TABLE 1 Baseline demographic and clinical characteristics of NPC patients by race/ethnicity groups (SEER 18, 1975-2018) (N = 11 964)[a,b,c]

	Total	NHW	NHB	Hispanics	Chinese	Filipino	Vietnamese	Hawaiian	Japanese	Laotian	Korean	Cambodian	Indian/ Pakistani	Other APIs	*P*-value[d]
	# (%)	4970 (41.5)	1312 (11.0)	870 (7.3)	2206 (18.4)	924 (7.7)	592 (5.0)	141 (1.2)	114 (1.0)	94 (0.8)	90 (0.8)	69 (0.6)	62 (0.5)	520 (4.4)	
Age at diagnosis (years), # (%)															<.0001
15-39	1892 (15.8)	518 (10.4)	294 (22.4)	202 (23.2)	424 (19.2)	130 (14.1)	109 (18.4)	24 (17.0)	11 (9.6)	17 (18.1)	27 (30.0)	14 (20.3)	16 (25.8)	106 (20.4)	
40-49	2484 (20.8)	736 (14.8)	270 (20.6)	175 (20.1)	593 (26.9)	256 (27.7)	179 (30.2)	36 (25.5)	12 (10.5)	27 (28.7)	20 (22.2)	17 (24.6)	<11	156 (30.0)	
50-59	3250 (27.2)	1391 (28.0)	340 (25.9)	225 (25.9)	604 (27.4)	238 (25.8)	167 (28.2)	32 (22.7)	26 (22.8)	30 (31.9)	18 (20.0)	16 (23.2)	17 (27.4)	146 (28.1)	
60-69	2586 (21.6)	1344 (27.0)	252 (19.2)	162 (18.6)	372 (16.9)	163 (17.6)	90 (15.2)	33 (23.4)	37 (32.5)	<11	>10 (>10)	>10 (>20)	16 (25.8)	73 (14.0)	
70+	1752 (14.6)	981 (19.7)	156 (11.9)	106 (12.2)	213 (9.7)	137 (14.8)	47 (7.9)	16 (11.3)	28 (24.6)	<11	<11	<11	<11	39 (7.5)	
Sex, # (%)															.53
Male	8473 (70.8)	3532 (71.1)	935 (71.3)	604 (69.4)	1547 (70.1)	629 (68.1)	438 (74.0)	106 (75.2)	82 (71.9)	70 (74.5)	61 (67.8)	49 (71.0)	43 (69.4)	377 (72.5)	
Female	3491 (29.2)	1438 (28.9)	377 (28.7)	266 (30.6)	659 (29.9)	295 (31.9)	154 (26.0)	35 (24.8)	32 (28.1)	24 (25.5)	29 (32.2)	20 (29.0)	19 (30.6)	143 (27.5)	
Marital status at diagnosis, # (%)															<.0001
Unmarried	4137 (34.6)	1845 (37.1)	751 (57.2)	370 (42.5)	470 (21.3)	239 (25.9)	145 (24.5)	54 (38.3)	37 (32.5)	26 (27.7)	22 (24.4)	24 (34.8)	<11	144 (27.7)	
Married	7311 (61.1)	2912 (58.6)	496 (37.8)	466 (53.6)	1640 (74.3)	645 (69.8)	418 (70.6)	86 (61.0)	73 (64.0)	67 (71.3)	63 (70.0)	44 (63.8)	>50 (>80)	350 (67.3)	
Year of diagnosis, # (%)															<.0001
1975-1985	1180 (9.9)	660 (13.3)	109 (8.3)	45 (5.2)	248 (11.2)	53 (5.7)	<11	15 (10.6)	28 (24.6)	<11	<11	<11	<11	17 (3.3)	
1986-1995	1507 (12.6)	668 (13.4)	122 (9.3)	76 (8.7)	355 (16.1)	126 (13.6)	>50 (>5)	31 (22.0)	26 (22.8)	>50 (>5)	<11	<11	<11	23 (4.4)	
1996-2005	3416 (28.6)	1356 (27.3)	370 (28.2)	250 (28.7)	699 (31.7)	281 (30.4)	193 (32.6)	34 (24.1)	26 (22.8)	193 (32.6)	35 (38.9)	21 (30.4)	14 (22.6)	101 (19.4)	
2006-2018	5861 (49.0)	2286 (46.0)	711 (54.2)	499 (57.4)	904 (41.0)	464 (50.2)	341 (57.6)	61 (43.3)	34 (29.8)	341 (57.6)	44 (48.9)	42 (60.9)	47 (75.8)	379 (72.9)	
Stage at diagnosis, # (%)															<.0001
Localized	1276 (10.7)	629 (12.7)	107 (8.2)	71 (8.2)	266 (12.1)	68 (7.4)	53 (9.0)	11 (7.8)	15 (13.2)	< 11	< 11	<11	<11	42 (8.1)	
Regional	7171 (59.9)	2966 (59.7)	736 (56.1)	490 (56.3)	1385 (62.8)	612 (66.2)	367 (62.0)	79 (56.0)	75 (65.8)	> 40 (> 40)	>60 (>70)	>40 (>60)	>30 (>50)	277 (53.3)	
Distant	3517 (29.4)	1375 (27.7)	469 (35.7)	309 (35.5)	555 (25.2)	244 (26.4)	172 (29.1)	51 (36.2)	24 (21.1)	50 (53.2)	23 (25.6)	22 (31.9)	22 (35.5)	201 (38.7)	
Histology, # (%)															<.0001
KSCC	4456 (37.2)	2474 (49.8)	520 (39.6)	295 (33.9)	489 (22.2)	251 (27.2)	128 (21.6)	45 (31.9)	49 (43.0)	24 (25.5)	25 (27.8)	21 (30.4)	18 (29.0)	117 (22.5)	
DNKC	2282 (19.1)	736 (14.8)	251 (19.1)	166 (19.1)	472 (21.4)	230 (24.9)	173 (29.2)	30 (21.3)	22 (19.3)	23 (24.5)	22 (24.4)	11 (15.9)	17 (27.4)	129 (24.8)	
UNKC	2219 (18.5)	642 (12.9)	214 (16.3)	162 (18.6)	599 (27.2)	224 (24.2)	124 (20.9)	41 (29.1)	18 (15.8)	20 (21.3)	23 (25.6)	12 (17.4)	16 (25.8)	124 (23.8)	
Other[e]	3007 (25.1)	1118 (22.5)	327 (24.9)	247 (28.4)	646 (29.3)	219 (23.7)	167 (28.2)	25 (17.7)	25 (21.9)	27 (28.7)	20 (22.2)	25 (36.2)	11 (17.7)	150 (28.8)	
Tumor grade, # (%)															<.0001
I-III	5461 (45.6)	2677 (53.9)	603 (46.0)	376 (43.2)	802 (36.4)	379 (41.0)	227 (38.3)	57 (40.4)	57 (50.0)	36 (38.3)	33 (36.7)	22 (35.5)	28 (40.6)	164 (34.5)	
IV	3006 (25.1)	862 (17.3)	298 (22.7)	236 (27.1)	757 (34.3)	291 (31.5)	193 (32.6)	52 (36.9)	21 (18.4)	30 (31.9)	33 (36.7)	23 (33.3)	22 (35.5)	188 (36.2)	
Chemotherapy, # (%)															<.0001
No/unknown	4055 (33.9)	1958 (39.4)	399 (30.4)	236 (27.1)	754 (34.2)	264 (28.6)	131 (22.1)	55 (39.0)	60 (52.6)	21 (22.3)	21 (23.3)	18 (26.1)	<11	130 (25.0)	
Yes	7909 (66.1)	3012 (60.6)	913 (69.6)	634 (72.9)	1452 (65.8)	660 (71.4)	461 (77.9)	86 (61.0)	54 (47.4)	73 (77.7)	69 (76.7)	51 (73.9)	>50 (>80)	390 (75.0)	

(Continues)

TABLE 1 (Continued)

	Total	NHW	NHB	Hispanics	Chinese	Filipino	Vietnamese	Hawaiian	Japanese	Laotian	Korean	Cambodian	Indian/ Pakistani	Other APIs	*P*-value[d]
RT, # (%)															<.0001
No/unknown	1717 (14.4)	815 (16.4)	238 (18.1)	136 (15.6)	178 (8.1)	109 (11.8)	84 (14.2)	19 (13.5)	13 (11.4)	17 (18.1)	<11	<11	<11	81 (15.6)	
Yes	10 247 (85.6)	4155 (83.6)	1074 (81.9)	734 (84.4)	2028 (91.9)	815 (88.2)	508 (85.8)	122 (86.5)	101 (88.6)	77 (81.9)	>80 (>80)	>50 (>80)	>50 (>80)	439 (84.4)	
Surgery, # (%)															<.0001
No	8312 (69.5)	3144 (63.3)	983 (74.9)	670 (77.0)	1482 (67.2)	700 (75.8)	485 (81.9)	86 (61.0)	56 (49.1)	>80 (>90)	77 (85.6)	58 (84.1)	>50 (>80)	434 (83.5)	
Yes	3652 (30.5)	1826 (36.7)	329 (25.1)	200 (23.0)	724 (32.8)	224 (24.2)	107 (18.1)	55 (39.0)	58 (50.9)	<11	13 (14.4)	11 (15.9)	<11	86 (16.5)	

Abbreviations: APIs, Asian/Pacific Islanders; DNKC, differentiated non-keratinizing carcinoma; KSCC, keratinizing squamous cell carcinoma; NHB, non-Hispanic Black; NHW, non-Hispanic White; NPC, nasopharyngeal cancer; RT, radiation therapy; UNKC, undifferentiated non-keratinizing carcinoma.

[a]Data from fewer than 11 patients were masked to maintain patient confidentiality.

[b]Vietnamese, Cambodian, Korean, Laotian cases were separate and captured by SEER only after year of 1988.

[c]Column totals may not add to total due to missing data.

[d]Chi-square test was used to compute the *P*-value.

[e]Other histology included carcinoma, not other specified, malignant tumors of bone, lymphomas and other non-epithelial tissues.

age-standardization.[21] Joinpoint Trend Analysis Software was used to calculate annual percentage change (APC) and its *P*-value.[22]

Chi-square tests were used to compare demographic and clinical-pathologic features across racial/ethnic groups. Multivariate Cox regression and Fine-Gray subdistribution hazard models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for overall and cause-specific mortalities after adjusting for demographic and clinical-pathologic factors.[23] The primary outcome was overall mortality, which was defined as the time from primary diagnosis to death due to any cause, or cut-off of the study analysis (31 December 2018) whichever came first. Cause-specific mortality was defined as the time from primary diagnosis to death due to NPC, cardiovascular diseases (CVD) or other cancers (excluding NPC) or cut-off of the study analysis. The proportional hazards assumption was examined by creating a time-by-race interaction variable via introducing products between race and a linear function of time.[24] If the assumption was violated, the time-by-race interaction term was kept in the final models. NHW was used as the reference group in the main analyses as it is the majority population in the United States (>50%).[25] Sensitivity analyses that were limited to AAs using Chinese as the reference group was also performed. Age at diagnosis, sex, marital status at diagnosis, year of diagnosis, stage, histology, grade, chemotherapy, RT and surgery were controlled in the adjusted Cox proportional models, as they were either known confounders between race/ethnicity and survival outcomes or had statistically significant difference by race/ethnicity groups in Table 1.[26-29] Bonferroni-Holm method was used to account for multiple group comparisons.[30] Listwise deletion methods were used to address missing data. The analysis was conducted using SAS 9.4 (SAS Institute, Cary, North Carolina). Results were considered statistically significant when two-sided *P*-values were <.05.

3 | RESULTS

Among the total 11 964 NPC cases, 18.4% were Chinese, 7.7% Filipino, 5.0% Vietnamese, 1.2% Hawaiian, 1.0% Japanese, 0.8% Laotian, 0.8% Korean, 0.6% Cambodian, 0.5% Indian/Pakistani and 4.4% other APIs (Table 1). Across all racial/ethnic subgroups, statistically significant differences were found in age, marital status and year of diagnosis. Laotians had the highest proportion of being diagnosed at the distant stage (53.2%). Nearly 50% of NHWs were diagnosed with KSCC histology, followed by Japanese (43.0%) whereas the percentage was lower in other AA subgroups (21.6%-31.9%) ($P < .0001$). All AA subgroups except for Japanese had higher proportions of grade IV tumor (>30%) compared to NHWs ($P < .0001$). Statistically significant differences were also observed in chemotherapy, RT and surgery (all *P*-values <.0001).

In terms of NPC incidence across racial and ethnic groups, Laotians had the highest AAIR—9.21 per 100 000 (Tables 2 and S2). The NPC incidences were significantly higher in Laotians (IRR = 18.04; 95% CI: 14.55-22.13) and Chinese (IRR = 13.08; 95% CI: 12.40-13.80) than NHWs but not in Japanese (IRR = 1.55; 95% CI:

TABLE 2 Age-adjusted NPC incidence (per 100 000) and 95% CI comparing racial and ethnic groups overall and by year of diagnosis, age, sex and histologic type (SEER 9, 1990-2014)

	NHW	NHB	Hispanics	Chinese	Filipino	Vietnamese	Hawaiian	Japanese	Laotian	Korean	Cambodian	Indian/Pakistani
AAIR[a]	0.51 (0.50-0.53)	0.80 (0.73-0.87)	0.50 (0.45-0.55)	6.68 (6.39-6.98)	3.20 (2.99-3.42)	5.15 (4.72-5.62)	2.48 (2.05-2.98)	0.59 (0.47-0.72)	9.21 (7.45-11.28)	0.85 (0.68-1.04)	4.93 (3.75-6.35)	0.52 (0.39-0.69)
IRR[b]	REF	1.69 (1.51-1.84)	1.03 (0.93-1.15)	13.08 (12.40-13.80)	6.26 (5.82-6.73)	10.09 (9.19-11.06)	4.86 (4.00-5.85)	1.15 (0.93-1.41)	18.04 (14.55-22.13)	1.66 (1.34-2.04)	9.64 (7.33-12.47)	1.02 (0.76-1.34)
APC[c,d,e]	−1.29%	−0.78%	−0.79%	−3.13%	−1.58%	−2.66%	−2.52%	0.31%	−2.65%	−3.41%	1.12%	−1.86%
P-value for APC	<.001	.17	.23	<.001	<.01	<.01	.01	.82	.05	.02	.50	.26
Year of diagnosis												
1990-1995	0.59 (0.56-0.63)	0.85 (0.61-1.07)	0.60 (0.45-0.77)	9.10 (8.23-10.03)	3.71 (3.16-4.33)	6.46 (5.09-8.13)	3.61 (2.41-5.24)	0.68 (0.43-1.03)	10.08 (5.85-16.55)	1.12 (0.66-1.81)	4.19 (2.09-8.27)	0.70 (0.31-1.50)
1996-2005	0.51 (0.49-0.54)	0.85 (0.74-0.97)	0.47 (0.40-0.56)	7.37 (6.88-7.90)	3.46 (3.11-3.84)	5.56 (4.80-6.41)	2.32 (1.64-3.18)	0.57 (0.40-0.80)	11.01 (7.94-14.91)	1.04 (0.74-1.42)	6.52 (4.08-9.79)	0.50 (0.29-0.81)
2006-2014	0.47 (0.44-0.49)	0.74 (0.64-0.85)	0.49 (0.43-0.57)	5.35 (4.97-5.76)	2.80 (2.51-3.10)	4.49 (3.94-5.11)	2.17 (1.59-2.89)	0.57 (0.40-0.79)	7.55 (5.29-10.47)	0.64 (0.44-0.90)	4.07 (2.71-5.91)	0.50 (0.33-0.72)
Age												
≤39	0.12 (0.11-0.13)	0.29 (0.24-0.36)	0.15 (0.12-0.18)	2.59 (2.33-2.88)	0.94 (0.78-1.11)	1.73 (1.42-2.08)	0.74 (0.46-1.13)	0.19 (0.09-0.35)	2.41 (1.44-3.75)	0.40 (0.26-0.60)	1.78 (0.99-2.90)	0.16 (0.09-0.28)
40-49	0.40 (0.37-0.44)	0.91 (0.76-1.08)	0.35 (0.28-0.44)	9.41 (8.63-10.23)	4.37 (3.84-4.95)	7.08 (6.03-8.25)	2.66 (1.74-3.89)	0.38 (0.18-0.70)	11.84 (8.05-16.81)	1.04 (0.67-1.55)	5.64 (3.34-8.91)	0.25 (0.10-0.51)
50-59	0.85 (0.80-0.91)	1.15 (0.96-1.38)	0.76 (0.63-0.92)	11.70 (10.72-12.74)	5.17 (4.53-5.88)	9.03 (7.64-10.59)	3.79 (2.50-5.51)	0.75 (0.43-1.20)	20.21 (14.08-28.11)	1.22 (0.76-1.87)	6.59 (3.69-10.86)	1.27 (0.80-1.90)
60-69	1.30 (1.23-1.38)	1.59 (1.29-1.95)	1.12 (0.90-1.38)	12.05 (10.8-13.4)	5.73 (4.89-6.68)	8.30 (6.59-10.31)	6.45 (4.25-9.40)	1.67 (1.13-2.39)	13.06 (6.73-22.90)	1.82 (1.09-2.84)	9.09 (4.51-16.31)	1.18 (0.63-2.03)
≥70	1.17 (1.10-1.24)	1.52 (1.21-1.89)	1.25 (0.99-1.56)	7.57 (6.59-8.65)	5.56 (4.67-6.57)	7.96 (5.98-10.39)	4.18 (2.43-6.67)	1.39 (0.95-1.96)	14.72 (7.01-27.37)	1.04 (0.47-2.02)	10.57 (4.76-20.42)	0.94 (0.33-2.13)
Sex												
Male	0.75 (0.72-0.78)	1.26 (1.13-1.40)	0.71 (0.62-0.80)	10.02 (9.49-10.56)	5.06 (4.67-5.48)	7.67 (6.91-8.50)	4.35 (3.50-5.35)	0.94 (0.73-1.19)	13.52 (10.35-17.37)	1.21 (0.91-1.57)	7.58 (5.49-10.25)	0.78 (0.54-1.08)
Female	0.30 (0.28-0.31)	0.44 (0.37-0.51)	0.32 (0.27-0.37)	3.81 (3.52-4.13)	1.81 (1.60-2.03)	2.79 (2.35-3.28)	0.85 (0.53-1.29)	0.33 (0.22-0.47)	5.14 (3.43-7.44)	0.58 (0.40-0.80)	2.62 (1.52-4.19)	0.26 (0.14-0.43)
Histology												
KSCC	0.24 (0.23-0.26)	0.33 (0.29-0.38)	0.16 (0.13-0.19)	1.42 (1.29-1.57)	0.84 (0.74-0.96)	1.26 (1.05-1.50)	0.84 (0.60-1.15)	0.23 (0.16-0.31)	2.69 (1.79-3.89)	0.23 (0.15-0.34)	1.44 (0.83-2.32)	0.17 (0.09-0.29)
DNKC	0.07 (0.06-0.07)	0.14 (0.11-0.17)	0.07 (0.06-0.09)	1.24 (1.12-1.38)	0.66 (0.57-0.76)	1.12 (0.92-1.35)	0.45 (0.28-0.69)	0.10 (0.06-0.16)	2.04 (1.22-3.19)	0.16 (0.09-0.27)	0.73 (0.36-1.34)	0.08 (0.04-0.15)
UNKC	0.07 (0.06-0.07)	0.12 (0.09-0.15)	0.09 (0.07-0.11)	1.74 (1.59-1.90)	0.82 (0.72-0.93)	1.15 (0.95-1.38)	0.72 (0.50-1.01)	0.12 (0.07-0.18)	1.75 (1.08-2.72)	0.19 (0.12-0.29)	0.91 (0.49-1.59)	0.14 (0.07-0.23)
Other[f]	0.13 (0.12-0.14)	0.22 (0.18-0.25)	0.18 (0.15-0.21)	2.28 (2.11-2.45)	0.88 (0.77-0.99)	1.62 (1.38-1.89)	0.47 (0.29-0.71)	0.14 (0.09-0.22)	2.73 (1.80-3.97)	0.26 (0.18-0.38)	1.85 (1.12-2.85)	0.14 (0.08-0.23)

Abbreviations: AAIR, age-adjusted incidence rate; APC, annual percentage change; APIs, Asian/Pacific Islanders; DNKC, differentiated non-keratinizing carcinoma; KSCC, keratinizing squamous cell carcinoma; IRR, incidence rate ratio; NHB, non-Hispanic Black; NHW, non-Hispanic White; NPC, nasopharyngeal cancer; REF, Reference; UNKC, undifferentiated non-keratinizing carcinoma.

[a]Rates are per 100 000 and age-adjusted to the 2000 US Std Population (18 age groups—Census P25-1130) standard; Confidence intervals (Tiwari modification) are 95% for rates.

[b]Results are statistically significant when the incidence rate ratio does not cross 1.

[c]APC and its associated *P*-values were calculated using the NCI Joinpoint Trend Analysis Software.

[d]Year 1998, 1999, 2009 and 2014 were not included when calculating APC for Indian/Pakistani, Hawaiian, Cambodian and Japanese, respectively, because no cases in above years were collected by the SEER for each corresponding Asian ethnic groups.

[e]Incidence calculation for NHB and Hispanics used data from SEER 13 (1992-2014) because the SEER 9 (1990-2014) data does not include NHB and Hispanic groups.

[f]Other histology included carcinoma, not other specified, malignant tumors of bone, lymphomas and other non-epithelial tissues.

TABLE 3 NPC treatment by racial and ethnic groups, stratified by stage at diagnosis (SEER 18, 1975-2018)[a]

	NHW	NHB	Hispanics	Chinese	Filipino	Vietnamese	Hawaiian	Japanese	Laotian	Korean	Cambodian	Indian/Pakistani	Other API	*P*-value[b]
Locoregional (n = 8447), # (%)														
RT														<.0001
Yes	3081 (85.7)	713 (84.6)	480 (85.6)	1556 (94.3)	610 (89.7)	377 (89.8)	78 (86.7)	>80 (>90)	>30 (>80)	>60 (>90)	>40 (>80)	>30 (>90)	291 (91.2)	
No/unknown	514 (14.3)	130 (15.4)	81 (14.4)	95 (5.8)	70 (10.3)	43 (10.2)	12 (13.3)	<11	<11	<11	<11	<11	28 (8.8)	
Chemotherapy														<.0001
Yes	2055 (57.2)	563 (66.8)	377 (67.2)	1000 (60.6)	460 (67.7)	313 (74.5)	48 (53.3)	38 (42.2)	33 (75.0)	52 (77.6)	32 (68.1)	>30 (>80)	226 (70.9)	
No/unknown	1540 (42.8)	280 (33.2)	184 (32.8)	651 (39.4)	220 (32.4)	107 (25.5)	42 (46.7)	52 (57.8)	11 (25.0)	15 (22.4)	15 (31.9)	<11	93 (29.2)	
Surgery														<.0001
Yes	1432 (39.8)	603 (71.5)	410 (73.1)	603 (36.5)	187 (27.5)	93 (22.1)	42 (46.7)	47 (52.2)	<11	11 (16.4)	<11	<11	64 (20.1)	
No	2163 (60.2)	240 (28.5)	151 (26.9)	1048 (63.5)	493 (72.5)	327 (77.9)	48 (53.3)	43 (47.8)	>30 (>80)	56 (83.6)	>30 (>80)	>30 (>80)	255 (79.9)	
Distant (n = 3517), # (%)														
RT														<.01
Yes	1074 (78.1)	361 (77.0)	254 (82.2)	472 (85.1)	205 (84.0)	131 (76.2)	>40 (>80)	>20 (>80)	38 (76.0)	>10 (>70)	>10 (>70)	>10 (>80)	148 (73.6)	
No/unknown	301 (21.9)	108 (23.0)	55 (17.8)	83 (15.0)	39 (16.0)	41 (23.8)	<11	<11	12 (24.0)	<11	<11	<11	53 (26.4)	
Chemotherapy														<.0001
Yes	957 (69.6)	350 (74.6)	257 (83.2)	452 (81.4)	200 (82.0)	148 (86.1)	38 (74.5)	>10 (>60)	>30 (>70)	>10 (>70)	>10 (>80)	>10 (>80)	164 (81.6)	
No/unknown	418 (30.4)	119 (25.4)	52 (16.8)	103 (18.6)	44 (18.0)	24 (14.0)	13 (25.5)	<11	<11	<11	<11	<11	37 (18.4)	
Surgery														<.0001
Yes	394 (28.7)	89 (19.0)	49 (15.9)	121 (21.8)	37 (15.2)	14 (8.1)	13 (25.5)	11 (45.8)	<11	<11	<11	<11	22 (11.0)	
No	981 (71.4)	380 (81.0)	260 (84.1)	434 (78.2)	207 (84.8)	158 (91.9)	38 (74.5)	13 (54.2)	>40 (>90)	>20 (>90)	>10 (>80)	>10 (>80)	179 (89.1)	

Abbreviations: APIs, Asian/Pacific Islanders; NHB, non-Hispanic Black; NHW, non-Hispanic White; NPC, nasopharyngeal cancer.

[a]Data from fewer than 11 patients were masked to maintain patient confidentiality.

[b]Chi-square test was used to compute the *P*-value.

TABLE 4 Overall mortality and cause-specific mortality by race and ethnic groups in NPC patients, stratified by sex (SEER 18, 1975-2018)[a,b]

	Overall[c]			Female[d]			Male[d]		
	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[e]	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[e]	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[e]
Overall mortality									
NHW	REF			REF			REF		
NHB	1.13 (1.03-1.24)	.01	.75	1.19 (1.00-1.42)	.05	1.00	1.10 (0.98-1.23)	.10	1.00
Hispanic	0.96 (0.86-1.08)	.51	1.00	0.96 (0.77-1.20)	.73	1.00	0.96 (0.84-1.10)	.59	1.00
Chinese	0.81 (0.74-0.88)	<.0001	<.0001	0.75 (0.64-0.88)	<.001	.04	0.84 (0.76-0.92)	<.001	.02
Filipino	0.76 (0.68-0.86)	<.0001	<.001	0.58 (0.46-0.73)	<.0001	<.001	0.85 (0.74-0.97)	.02	1.00
Vietnamese	0.92 (0.79-1.06)	.25	1.00	0.67 (0.48-0.94)	.02	1.00	1.01 (0.86-1.19)	.87	1.00
Hawaiian	0.96 (0.75-1.22)	.72	1.00	1.00 (0.60-1.65)	.99	1.00	0.93 (0.70-1.23)	.61	1.00
Japanese	1.04 (0.81-1.34)	.77	1.00	1.06 (0.64-1.74)	.83	1.00	1.05 (0.78-1.41)	.77	1.00
Laotian	1.55 (1.15-2.09)	<.01	.29	1.18 (0.65-2.16)	.59	1.00	1.69 (1.20-2.39)	<.01	.21
Korean	0.68 (0.46-0.99)	.04	1.00	0.46 (0.22-0.97)	.04	1.00	0.79 (0.51-1.23)	.30	1.00
Cambodian	0.96 (0.66-1.41)	.84	1.00	1.18 (0.56-2.50)	.66	1.00	0.91 (0.58-1.41)	.66	1.00
Indian/Pakistani	0.62 (0.35-1.09)	.10	1.00	0.19 (0.03-1.33)	.09	1.00	0.80 (0.44-1.45)	.45	1.00
Other APIs	0.85 (0.72-1.00)	.05	1.00	0.80 (0.57-1.11)	.18	1.00	0.87 (0.71-1.05)	.15	1.00
NPC-specific mortality									
NHW	REF			REF			REF		
NHB	1.01 (0.87-1.17)	.88	1.00	1.03 (0.78-1.36)	.84	1.00	0.99 (0.83-1.19)	.95	1.00
Hispanic	1.05 (0.88-1.24)	.59	1.00	1.18 (0.87-1.59)	.30	1.00	1.00 (0.81-1.22)	.96	1.00
Chinese	1.27 (1.14-1.42)	<.0001	<.01	1.14 (0.91-1.42)	.26	1.00	1.32 (1.16-1.50)	<.0001	<.01
Filipino	1.08 (0.92-1.27)	.32	1.00	0.81 (0.58-1.12)	.20	1.00	1.20 (1.00-1.44)	.05	1.00
Vietnamese	1.26 (1.04-1.53)	.02	1.00	0.93 (0.62-1.41)	.74	1.00	1.39 (1.12-1.72)	<.01	.19
Hawaiian	1.14 (0.82-1.57)	.44	1.00	1.23 (0.65-2.31)	.53	1.00	1.10 (0.75-1.60)	.63	1.00
Japanese	1.09 (0.74-1.62)	.66	1.00	1.18 (0.57-2.48)	.66	1.00	1.07 (0.68-1.70)	.77	1.00
Laotian	1.49 (1.00-2.23)	.05	1.00	1.54 (0.71-3.34)	.28	1.00	1.47 (0.91-2.38)	.11	1.00
Korean	1.29 (0.88-1.88)	.19	1.00	1.02 (0.51-2.05)	.96	1.00	1.39 (0.89-2.19)	.15	1.00
Cambodian	1.81 (1.19-2.77)	.01	.45	1.77 (0.74-4.25)	.20	1.00	1.85 (1.14-3.00)	.01	.95
Indian/Pakistani	1.08 (0.60-1.96)	.80	1.00	0.42 (0.07-2.46)	.33	1.00	1.34 (0.70-2.54)	.38	1.00
Other APIs	1.20 (0.97-1.50)	.10	1.00	1.27 (0.83-1.96)	.27	1.00	1.17 (0.90-1.51)	.25	1.00
CVD-specific mortality									
NHW	REF			REF			REF		
NHB	1.53 (1.14-2.06)	.01	.39	1.94 (1.11-3.39)	.02	.82	1.40 (0.98-1.99)	.06	1.00

(Continues)

TABLE 4 (Continued)

	Overall[c]			Female[d]			Male[d]		
	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[e]	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[e]	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[e]
Hispanic	0.90 (0.59-1.37)	.61	1.00	1.06 (0.47-2.41)	.88	1.00	0.81 (0.48-1.35)	.41	1.00
Chinese	0.89 (0.68-1.17)	.40	1.00	1.07 (0.62-1.85)	.80	1.00	0.85 (0.62-1.16)	.30	1.00
Filipino	0.93 (0.63-1.38)	.72	1.00	1.17 (0.56-2.44)	.67	1.00	0.87 (0.55-1.38)	.56	1.00
Vietnamese	0.83 (0.47-1.47)	.53	1.00	NA	NA	NA	1.04 (0.58-1.86)	.89	1.00
Hawaiian	1.09 (0.49-2.43)	.82	1.00	1.03 (0.13-7.95)	.98	1.00	1.10 (0.46-2.59)	.84	1.00
Japanese	0.44 (0.14-1.35)	.15	1.00	NA	NA	NA	0.55 (0.18-1.68)	.29	1.00
Laotian	0.94 (0.23-3.93)	.94	1.00	2.30 (0.27-19.94)	.45	1.00	0.61 (0.08-4.41)	.62	1.00
Korean	0.97 (0.24-3.97)	.96	1.00	2.22 (0.30-16.33)	.43	1.00	0.63 (0.09-4.64)	.65	1.00
Cambodian	1.08 (0.33-3.55)	.90	1.00	NA	NA	NA	1.33 (0.41-4.29)	.63	1.00
Indian/Pakistani	1.10 (0.15-7.95)	.92	1.00	NA	NA	NA	1.42 (0.19-10.42)	.73	1.00
Other APIs	0.87 (0.45-1.68)	.67	1.00	0.41 (0.07-2.54)	.34	1.00	1.00 (0.49-2.04)	.99	1.00
Cancer-specific mortality									
NHW	REF			REF			REF		
NHB	1.05 (0.88-1.24)	.60	1.00	1.21 (0.88-1.65)	.24	1.00	1.00 (0.82-1.23)	.98	1.00
Hispanic	0.90 (0.73-1.12)	.36	1.00	0.76 (0.49-1.17)	.21	1.00	0.98 (0.76-1.26)	.85	1.00
Chinese	0.39 (0.32-0.47)	<.0001	<.0001	0.32 (0.21-0.48)	<.0001	<.0001	0.42 (0.33-0.53)	<.0001	<.0001
Filipino	0.41 (0.31-0.55)	<.0001	<.0001	0.26 (0.14-0.51)	<.0001	<.01	0.47 (0.34-0.65)	<.0001	<.001
Vietnamese	0.53 (0.38-0.73)	<.001	.01	0.18 (0.06-0.56)	<.01	.13	0.64 (0.45-0.91)	.01	.80
Hawaiian	0.78 (0.47-1.29)	.34	1.00	0.56 (0.17-1.88)	.34	1.00	0.85 (0.49-1.47)	.55	1.00
Japanese	1.12 (0.71-1.77)	.64	1.00	1.19 (0.48-2.97)	.71	1.00	1.10 (0.65-1.88)	.71	1.00
Laotian	0.78 (0.40-1.53)	.47	1.00	NA	NA	NA	1.14 (0.58-2.23)	.70	1.00
Korean	0.37 (0.15-0.96)	.04	1.00	NA	NA	NA	0.56 (0.22-1.41)	.22	1.00
Cambodian	0.44 (0.17-1.18)	.10	1.00	0.44 (0.06-3.30)	.43	1.00	0.44 (0.14-1.36)	.15	1.00
Indian/Pakistani	0.18 (0.03-1.27)	.09	1.00	NA	NA	NA	0.25 (0.04-1.72)	.16	1.00
Other APIs	0.50 (0.34-0.74)	<.001	.03	0.43 (0.19-0.96)	.04	1.00	0.54 (0.34-0.83)	.01	.39

Abbreviations: APIs, Asian/Pacific Islanders; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NHB, non-Hispanic Black; NHW, non-Hispanic White; NPC, nasopharyngeal cancer; REF, Reference.

[a]Vietnamese, Cambodian, Korean, Laotian cases were separate and captured by SEER only after year of 1988.

[b]NA indicates that no death due corresponding cause was captured by SEER. Therefore, cause-specific mortality could not be calculated.

[c]Model d + sex.

[d]Model adjusted for age, marital status, stage, grade, histology, radiation, chemotherapy and surgery.

[e]Holm-adjusted *P*-value is calculated to account for multiple comparisons.

TABLE 5 Overall mortality and NPC-specific mortality in NPC patients, stratified by histology (SEER 18, 1975-2018)[a,b]

	KSCC			DNKC			UNKC		
	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[c]	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[c]	HR (95% CI)	Unadjusted *P*-value	Holm-adjusted *P*-value[c]
Overall mortality									
NHW	REF			REF			REF		
NHB	1.08 (0.94-1.23)	.28	1.00	1.07 (0.82-1.38)	.63	1.00	1.39 (1.09-1.76)	.01	.59
Hispanic	0.99 (0.83-1.18)	.91	1.00	1.05 (0.78-1.42)	.76	1.00	1.03 (0.79-1.36)	.81	1.00
Chinese	0.78 (0.67-0.89)	<.001	.02	0.88 (0.71-1.08)	.22	1.00	0.88 (0.74-1.04)	.13	1.00
Filipino	0.72 (0.59-0.87)	<.001	.06	0.76 (0.58-1.01)	.06	1.00	0.90 (0.71-1.15)	.41	1.00
Vietnamese	1.02 (0.78-1.33)	.90	1.00	0.94 (0.67-1.32)	.71	1.00	0.94 (0.70-1.28)	.70	1.00
Hawaiian	0.97 (0.64-1.49)	.90	1.00	1.09 (0.56-2.15)	.79	1.00	1.06 (0.71-1.58)	.79	1.00
Japanese	1.02 (0.72-1.46)	.90	1.00	1.11 (0.49-2.54)	.80	1.00	1.25 (0.70-2.23)	.46	1.00
Laotian	1.94 (1.20-3.14)	.01	.50	1.45 (0.74-2.85)	.28	1.00	1.27 (0.65-2.48)	.49	1.00
Korean	0.66 (0.35-1.23)	.19	1.00	0.96 (0.42-2.20)	.93	1.00	0.65 (0.30-1.37)	.25	1.00
Cambodian	0.84 (0.45-1.57)	.58	1.00	1.16 (0.48-2.84)	.74	1.00	1.02 (0.42-2.49)	.96	1.00
Indian/Pakistani	1.22 (0.58-2.58)	.59	1.00	0.22 (0.03-1.56)	.13	1.00	0.40 (0.13-1.26)	.12	1.00
Other APIs	0.76 (0.55-1.05)	.09	1.00	0.99 (0.67-1.47)	.97	1.00	0.97 (0.69-1.35)	.85	1.00
NPC-specific mortality									
NHW	REF			REF			REF		
NHB	0.96 (0.78-1.20)	.74	1.00	0.87 (0.59-1.28)	.48	1.00	1.24 (0.86-1.79)	.24	1.00
Hispanic	1.12 (0.86-1.45)	.41	1.00	1.07 (0.72-1.57)	.75	1.00	0.95 (0.62-1.45)	.80	1.00
Chinese	1.41 (1.19-1.67)	<.0001	<.01	1.11 (0.84-1.47)	.46	1.00	1.30 (1.01-1.69)	.05	1.00
Filipino	1.17 (0.91-1.51)	.22	1.00	0.92 (0.64-1.33)	.66	1.00	1.31 (0.92-1.86)	.13	1.00
Vietnamese	1.39 (0.99-1.96)	.06	1.00	1.12 (0.74-1.72)	.59	1.00	1.37 (0.91-2.08)	.13	1.00
Hawaiian	0.99 (0.56-1.75)	.98	1.00	1.42 (0.71-2.86)	.33	1.00	1.07 (0.57-2.02)	.82	1.00
Japanese	1.00 (0.56-1.78)	.99	1.00	1.10 (0.38-3.15)	.86	1.00	1.18 (0.51-2.75)	.70	1.00
Laotian	2.29 (1.36-3.85)	<.01	.14	2.07 (0.96-4.46)	.06	1.00	0.54 (0.15-2.00)	.36	1.00
Korean	1.21 (0.63-2.30)	.57	1.00	1.89 (0.90-3.99)	.09	1.00	1.23 (0.54-2.84)	.62	1.00
Cambodian	1.86 (0.88-3.90)	.10	1.00	0.80 (0.22-2.90)	.74	1.00	2.38 (1.05-5.39)	.04	1.00
Indian/Pakistani	2.03 (0.99-4.17)	.05	1.00	0.43 (0.06-2.91)	.39	1.00	0.74 (0.21-2.60)	.64	1.00
Other APIs	1.32 (0.86-2.02)	.21	1.00	1.07 (0.67-1.71)	.79	1.00	1.29 (0.80-2.07)	.29	1.00

Abbreviations: APIs, Asian/Pacific Islanders; CI, confidence interval; HR, hazard ratio; DNKC, differentiated non-keratinizing carcinoma; KSCC, keratinizing squamous cell carcinoma; NHB, non-Hispanic Black; NHW, non-Hispanic White; NPC, nasopharyngeal cancer; REF, Reference; UNKC, undifferentiated non-keratinizing carcinoma.

[a]Model adjusted for age, sex, marital status, stage, grade, surgery, chemotherapy and radiation.

[b]Vietnamese, Cambodian, Korean, Laotian cases were separate and captured by SEER only after year of 1988.

[c]Holm-adjusted *P*-value is calculated to account for multiple comparisons.

0.93-1.41), Indians/Pakistanis (IRR = 1.02; 0.76-1.34) or Hispanics (IRR = 1.03; 95% CI: 0.93-1.15). Also, Koreans observed the most rapid decrease in NPC incidence from 1990 to 2014, with an APC of 3.41% ($P = .02$) followed by Chinese 3.13% ($P < .001$). No significant decreasing APC was found in Cambodians despite that their incidence was nearly 10 times higher than it in NHWs ($P = .50$). Besides, peak incidence age appeared to be younger in Laotians and Vietnamese than in other groups (50-59 vs >60 years, respectively) (Tables 2 and S3). Males had higher AAIRs than females across all race/ethnicity groups, with a male: female ratio ranging from 2 to 3 (Table S4). When stratified by histology type, the NPC incidence in Laotians was higher than it in NHWs across all histology groups with the most drastic difference found in DNKC (IRR = 30.41), followed by UNKC (for Laotians IRR = 25.65, for Chinese IRR = 25.45, respectively) (Table S4). Overall, 61.3% of patients received both chemotherapy and RT though the percentage varies between racial/ethnic subgroups (Table S5). In locoregional disease, more than 80% of patients underwent RT though with significant variations across all groups ($P < .0001$) (Table 3). More than 80% of Indians/Pakistanis had chemotherapy as their first-line therapy compared to 42.2% of Japanese. In distant disease, >80% of non-Japanese AA patients had chemotherapy compared to 69.6% in HNWs and >60% in Japanese ($P < .0001$).

Overall mortality and cause-specific mortality comparing different racial/ethnic groups were also shown in Table 4. Regarding overall mortality, after adjusting for multiple comparisons, Chinese and Filipinos had statistically significant decreases in overall mortality (HR = 0.81; 95% CI: 0.74-0.88 and HR = 0.76; 95% CI: 0.68-0.86, respectively) than NHWs and similar patterns were found in both genders of Chinese patients. Laotians had elevated overall mortality than NHWs (HR = 1.55; 95% CI: 1.15-2.09) but such difference was not significant after adjusting for multiple comparisons. Besides, Laotians had higher overall mortality than Chinese (HR = 2.19; 95% CI: 1.59-3.02, Holm-adjusted $P < .0001$) (Table S6). Regarding NPC-specific mortality, Chinese were at a 27% higher risk of death due to NPC than NHWs after adjusting for multiple comparisons, especially in males (Holm-adjusted $P < .01$). Numerically increased risks due to NPC were also found in Vietnamese, Laotian and Cambodian patients. No racial/ethnic differences were observed regarding CVD-specific mortality. Lastly, for other cancer-specific mortality, we found reduced risks in Chinese, Filipino, Vietnamese and other API patients than NHWs after adjusting for multiple comparisons (Holm-adjusted $P < .0001$, <.0001, .01 and <.001, respectively). Chinese patients with KSCC had lower overall (Holm-adjusted $P = .02$) but elevated NPC-specific mortality (Holm-adjusted $P < .01$, respectively) (Table 5). Besides, Laotian patients were at 2.64 times increased overall mortality than Chinese (Holm-adjusted $P = .01$) (Table S7).

4 | DISCUSSION

To our knowledge, this is the first and largest population-based study examining NPC disparities across AA subgroups. Results show significant heterogeneities in incidence, tumor stage, grade, histology, treatment and survival outcomes between AAs and other racial groups, as well as within AA subgroups. Though the AAIR of NPC has been declining since 1990, Laotians continued to have the highest incidence rate among all racial/ethnic groups, with more than 50% diagnosed at the distant stage. In comparison, Japanese and Indians/Pakistanis had similar NPC incidence rates to NHW. Chinese and Filipino NPC patients saw lower overall mortalities, but Chinese were at elevated risks of NPC-caused death than their NHW peers.

4.1 | Racial/ethnic disparities in NPC incidence

Significant racial/ethnic disparities exist in NPC incidence. Overall, the AAIR of NPC has been declining over the past two decades in NHWs and the majority of the AAs (albeit with various degrees) except for Japanese, Cambodians and Indians/Pakistanis. Continuously incoming younger immigrants with lower NPC incidence may partially contribute to the declining incidence.[2] Besides, length of immigration duration and subsequent adoption of a westernized lifestyle may also account for the discrepancies in the incidence rate.[31,32] For example, Vietnamese, Laotians and Cambodians had shorter immigration history (started in the 1970s) than other Asian ethnic groups[33] and they had approximately five times or higher NPC incidences than NHWs. Since Chinese and Filipinos have the longest documented immigration history (started in the 1600s) than other AA ethnic groups (Asian Indians [1790s], Japanese [1850s] and Koreans [1900s]), one may expect that they would have similar NPC incidence to NHW.[33] However, oppositive findings were observed that Chinese and Filipino had higher NPC incidences than NHW but not Japanese, Indians/Pakistanis or Koreans. Therefore, the changing risk profile after immigration, including modification in diet and health behaviors (eg, decreased intake of salted fish or preserved food and reduced tobacco consumption) does not solely depends on the duration of immigration, while other cultural factors also play important roles.[31,32] For instance, tobacco use is considered a cultural norm and tradition in Laotians and they continued to have the highest smoking prevalence (52%-72% in male and 11% in female) than other AAs such as Vietnamese (24% in male and 7.9% in female) and Filipinos (20.6% in male and 7.5% in female).[31,34] In addition, Chewing betel quid (containing betel leaves, areca nut, slaked lime and tobacco), which alone accounts for a third of head and neck cancers, is a common practice among Laotian females.[34]

The peak incidence age of Vietnamese and Laotians (50-59) was younger than other groups (60-69). The early onset may reflect the biological aggressiveness of NPC in Vietnamese and Laotian patients and possible genetic susceptibilities.[35] In addition, passive smoking exposure during childhood is also associated with an increased risk of NPC.[36] Males have a higher NPC incidence than females irrespective of country or region, which is consistent with previous studies.[26-28] Possible explanations include sex differences in environmental factors such as smoking and occupational exposures.[26] Besides, it has been shown that the sex difference in incidence declined after age 55 to 59, indicating hormonal factors may also play a role.[27]

Genetic susceptibility such as sex-based difference in gene expression and its potential interaction with Epstein-Barr virus (EBV) infections has also been suggested.[35] Therefore, the incidence disparity is likely a composite effect of behavioral and cultural factors, as well as tumor biology and genetic susceptibilities.[26-28,35]

4.2 | EBV exposure and NPC incidence

Endemic NPC is closely linked to EBV infection, which usually presents as UNKC compared to non-endemic regions where the KSCC is more common.[37] KSCC histology has a more aggressive biological behavior, which is featured by a higher risk of local recurrence, less sensitive to RT and platinum-based chemotherapy and worse overall and NPC-specific survival outcomes than UNKC.[16,38] Compared to NHWs, we found significantly elevated AAIR across all histology subtypes, especially in non-Japanese, and non-Indian/Pakistani AAs. Besides, it is worth noting that the histology and grade distribution of Japanese NPC cases were similar to their NHW peers. Hence, the pathogenesis of NPC is likely a combination of viral etiology, genetic disposition as well as cultural transmission of environmental exposures.[39,40] This conclusion is supported by the observation from a large migrant cohort of 2.3 million Jewish Israeli adolescents. In this study, birth origin was a strong independent predictor of developing NPC, and the increased risk of NPC in this population persisted in the first, second and third generations of Israeli immigrants from Asia even after controlling for confounders.[39] Currently there are no screening guidelines for early NPC detection. Circulating plasma EBV DNA has been suggested as a promising blood-based screening tool that could increase the proportion of early-stage NPC detection and improve progression-free survival.[41] Large prospective studies are needed to test this screening approach, especially in high-risk populations like AAs.

4.3 | Racial/ethnic disparities in treatment patterns and survival outcomes

RT is the backbone in the treatment of locoregional NPC whereas the mainstay treatment for the distant disease is systemic chemotherapy.[36,40] The explanation of treatment disparities may be limited by the small sample size in certain AA subgroups. Cultural beliefs play a critical role in the perception of cancer.[5] "Cancer" has been considered a stigma in many Asian countries leading to lower uptake of cancer screening, delayed diagnosis and suboptimal treatment.[42] It is possible that there is a variation in such perception by Asian ethnicity. Besides, according to national-level data, although AA overall had the lowest uninsured rate, significant heterogeneity within AAs exit.[43] Therefore, ethnicity and culture tailored care navigation for AA subgroups are needed to improve early NPC diagnosis and treatment.

Outcome studies in AA NPC patients that separating AAs into detailed ethnic subgroups has been rare.[6,8-13] We found that Chinese and Filipinos had decreased overall mortality than NHWs whereas elevated NPC-specific mortality was found in Chinese patients despite accounting for multiple comparisons. When limited to AAs, Laotians had increased overall mortality than Chinese. In addition to the differences in genetic and molecular levels (eg, a higher proportion of epidermal growth factor receptor [EGFR] polymorphism),[14,44] the "salmon bias" hypothesis may also explain the findings. It is defined as "foreign-born individuals return to their country of origin at terminal illness, and their deaths were not registered at the country where they reside, which results in a falsely low mortality rate."[45,46] Therefore, the heterogeneous treatment patterns and survival outcomes by race/ethnicity could be a complex interaction of physical fitness, access to care, immigration history, cultural beliefs, perception of disease and treatment, geographic locations and biological features of the disease.[47]

Due to shared risk factors, baseline comorbidity profile, genetic predisposition and exposure to chemotherapy and/or RT, NPC patients are at higher risk of developing secondary malignancies and CVD.[48] However, studies on health behavior and secondary malignancy outcomes among separate AA NPC survivors are rare. Reports in breast cancer survivors showed that AA women are more likely to increase their physical activity and enhance stress management skills after cancer diagnosis but are also more likely to report having barriers in accessing health information and potentially underuse cancer screening due to limited English proficiency and less effective communication with health care providers.[42,49] Hence, the heterogeneities in other cancer-specific mortalities in AA patients were likely multifactorial.

4.4 | Strengths and limitations

The SEER program provides long-term population-based cancer data, which allows for a comprehensive analysis of AA ethnic subgroups and a longitudinal follow-up extending beyond that of interventional clinical trials. Holm-adjustment was used to account for multiple comparisons. By limiting to AAs and subsequently decrease the denominator, the additional sensitivity analyses not only were able to measure the differences within AAs that otherwise would not be observed if using NHW as the reference group (especially for subgroups with small sample size), but also test the robustness of results. Several limitations should be noted. First, the SEER database has limited information (only the first course) on chemotherapy treatment and detailed regimen plans, which may impact the survival outcomes.[50] In NPC, surgery is not used as a first-line treatment at the primary site and is usually reserved for recurrent local and regional diseases.[36] As cancer recurrence was not captured by the SEER database, patients who had surgery may have different clinical courses and/or access to surgery than those who did not, potentially confounding the outcomes. Second, the SEER database did not capture adequate individual-level information (eg, education, smoking, comorbidity, EBV infection) which may lead to residual confounding. Besides, Vietnamese, Cambodian, Korean, Laotian ethnicity was not separated by the SEER database until 1988, which may lead to

potential selection bias and confounding such as changes in treatment over time.[2]

5 | CONCLUSION

In conclusion, we found significant disparities of NPC in incidence, diagnosis, treatment and mortality between AAs and other racial groups, as well as within AA subgroups. AAs have been historically studied as one aggregated racial group mostly due to limited sample size, despite being a diverse population. Our findings underline the importance of adequate AA-subgroup sample collection in future studies in order to understand the prognostic role of ethnicity in NPC and advocate for more ethnically and culturally tailored cancer prevention and care delivery.

AUTHOR CONTRIBUTIONS

Qian Wang contributed to conceptualization, methodology, formal analysis, writing original draft, reviewing & editing; Hui Xie contributed to conceptualization, methodology, data curation, formal analysis, writing original draft, reviewing & editing; Yannan Li contributed to conceptualization, reviewing & editing the draft; Nicholas Theodoropoulos contributed to conceptualization, reviewing & editing the draft; Yaning Zhang contributed to conceptualization, reviewing & editing the draft; Changchuan Jiang contributed to methodology and writing-reviewing & editing; Chi Wen contributed to methodology and writing-reviewing & editing; Laura S. Rozek contributed to writing-reviewing & editing, supervision; Paolo Boffetta contributed to conceptualization, reviewing & editing and supervision. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data were requested though the National Cancer Institute Surveillance, Epidemiology and End Results program and can be found at https://seer.cancer.gov/data/. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

The analysis was exempted from ethical review since the SEER database was open-access and de-identifiable (The detailed information of data could be found elsewhere: https://seer.cancer.gov/data/).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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