The racial disparity of nasopharyngeal carcinoma based on the database analysis

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ABSTRACT

Objective: To investigate whether the racial/ethnical disparity of nasopharyngeal carcinoma exists among the four major ethical groups in the United States named Asians, Caucasians, African Americans and Hispanics between the years of 1973 to 2013 using the Surveillance, Epidemiology, and End Result (SEER) database.
Methods: The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database from 1973 to 2013 was utilized in this study to calculate survival trends for the four main ethical groups in the United States. The cases of nasopharyngeal carcinoma were extracted based on the SEER code cs0204schema. Death due to the diagnosed nasopharyngeal cancer was considered to be the event of interest, and death due to other causes was treated as the censoring events. Kaplan–Meier model was adopted to estimate survival outcomes; the Cox proportional hazards model was employed to do the hazard ratios (HR) estimation.
Results: A total of 8068 eligible patients of nasopharyngeal carcinoma were identified. The cohort was composed of 40.69% Caucasians, 11.34% African Americans, 40.16% Asians and 7.81% Hispanics. According to the multivariate Cox regression analysis, Asians had a better survival prognosis against Caucasians (HR: 0.74, 95% CI: 0.65–0.84, $P < 0.001$). African Americans showed marginal worse survival prognosis compared with Caucasians (HR: 1.26, 95% CI: 1.07–1.49, $P < 0.005$). There was no significant difference between Hispanics and Caucasians (HR: 1.13, 95% CI: 0.92–1.39, $P = 0.261$).
Conclusion: Asians showed a disease specific survival advantage over Caucasians, African Americans and Hispanics, which was independent of sex, age at diagnosis, grade, TNM staging and treatment strategy.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumor in head and neck region, which has higher incidence rate in south China than in most other areas [1]. A number of studies have been conducted based on SEER database, which is the largest population based cancer registration in the United States and essential to clinical treatment strategy and research [2–5]. There have been certain studies investigated the racial disparities of NPC by SEER database or individual hospital-based studies, but the conclusions were in controversy [6–8].

Patel et al. [6] reported that African Americans and Asians with NPC had better disease specific survival compared with Caucasians by using the SEER database 1988–2010. Wang et al. [7] investigated the SEER database 1973–2009 comprehensively. After overall survival analysis being conducted with Kaplan–Meier (K–M) model, they concluded that racial differences exist among NPC patients in the United States. Asians had the highest rate of five-year survival rates.

Bhattacharyya [8] found difference between overall survival and disease specific survival that the Chinese patients' survival advantages disappeared in disease specific survival compared with overall survival. This suggested that merely took overall survival into consideration may not be adequate. Sun et al. [9] studied the SEER database and elucidated that, Chinese NPC patients in the United States have better overall survival and the same risks of NPC-related mortality compared with others. Ou et al. [10] claimed that Chinese ethnicity is an independent prognostic factor in NPC patients. However, this survival advantage is most likely due to better survival within the keratinizing squamous cell carcinoma. Bhattacharyya [8] studied the SEER database 1988–2000 and made matched analysis, coming to the conclusion that overall survival is better for Chinese patients with NPC compared with White patients, with the exception of disease-specific. Shavers et al. [11] obtained data from the SEER database 1997, but statistically differences was not found either in overall or cancer-specific survival between African Americans and whites who have cancers of the oral

cavity and pharynx.

In conclusion, the existed studies showed possible disparities in racial and ethnical which may be the independent prognostic factor to NPC. The published references used overall survival, cancer-specific survival or disease specific survival analysis in different studies and drew different results [6,11]. Sun et al. used cause-specific analyze, but they used the SEER database (1973–2002).Currently, Ning et al. studied the overall survival and cause-specific mortality of elderly women in breast cancer survival [12]. However, the cause-specific mortality in NPC was seldom investigated. Thus, currently update of the database warrant our study. Therefore, in this study overall survival, disease specific survival and cause-specific survival were analyzed about NPC in the SEER database (1988–2013) with the aim of testing whether survival benefit of Asians existed.

2. Materials and methods

2.1. Study population

There were 12,380 patients registered with NPC in SEER database. The cutoff date of follow-up for the Nov 2015 submission in this analysis was Dec 2013. The flowchart of this cohort selection was summarized in Fig. 1. When unknown survival time, demographic information, age at diagnosis equal to 0 or 999 were excluded, meanwhile the patients who suffered only first primary and one tumor in the lifetime were kept, 9618 cases were reserved. Those who diagnosed base on autopsy or death certification only were excluded. Finally, we selected 8068 patients with the diagnosis year in 1988 or later. This study with no need for ethics committee approval because the data is publicly available.

2.2. Varieties and covariates

The following characteristics were extracted from this cohort study: patients' identifier number, gender, age at diagnosis, year at diagnosis, tumor size, lymph node involvement, metastasis, surgical treatment, radiation used, order of surgery and radiation, race and ethnicity,

SEER 1973-2013
Nasopharyngeal cancer
n=12380

Omit NA data in survival time, demographic information and chose only first primary tumor and one tumor in the lifetime. Age at diagnosis equal to 0 or 999 were excluded also. No cases were autopsy or death certificated only.
n = 9618

1988 - 2013 Nasopharyngeal cancer
n = 8068

Fig. 1. Flow diagram of patients' refinement.

survival time, vital status recode, sequence number, histology type, grade, source of report and cause of death.

2.3. Statistical analysis

Perl (ActivePerl-5.24.0) was applied to do the data extraction; R (v3.4.2) was conducted to do the statistical analyses, $P < 0.05$ was defined as statistically significant. First, data were extracted, refined in R; and the descriptive analyses were utilized to evaluate the disparity of patients in Caucasians, African Americans, Asians and Hispanics. Then, Kaplan–Meier model was employed to estimate the survival outcomes of these four racial/ethnical groups. Finally, in order to evaluate the influence of each interested variable, the univariate and multivariate Cox proportional hazards models were constructed to calculate HRs and 95% confidence intervals (CI).

3. Results

3.1. Descriptive information of different racial/ethnical groups

The descriptive characteristics of these four major racial/ethnical groups were listed in Table 1. Overall 8068 patients were chosen to do the final analysis. 3283, 915, 3240 and 630 were Caucasians, African Americans, Asians and Hispanics, respectively. The mean age at diagnosis were (56.6 ± 16.96), (48.52 ± 18.40), (51.25 ± 13.92) and (48.28 ± 18.70). The family-wise confidence level indicated that the mean age at diagnosis of Caucasians was older than African Americans ($p < 0.001$), Asians ($p < 0.001$), and Hispanics ($p < 0.001$). The mean age at diagnosis of Asians was older than Hispanics ($p < 0.001$) and African Americans ($p < 0.001$) (Fig. 2A, B.).Male to female ratio was 2.30 in Caucasians and 2.45 , 2.34 , 2.20 in African Americans, Asians and Hispanics, respectively, no racial/ethnical disparity was found ($p = 0.78$).

The mean tumor size were (41.70 ± 38.34) mm, (42.31 ± 18.38) mm, (36.43 ± 25.36) mm and (47.56 ± 67.46)mm for Caucasians, African Americans, Asians and Hispanics, respectively ($p = 0.69$) (Fig. 2C, D). The mean tumor size of Asians were slightly smaller than Caucasians ($p = 0.01$) and Hispanics ($p < 0.001$) (Fig. 2D).The lymph node involvement has no statistically significant among these four racial groups, which was 62.75%, 69.17%, 72.91% and 66.67% for Caucasians, African Americans, Asians and Hispanics, respectively ($p = 0.69$).

The histology type of these four racial/ethnical groups implied that the Asians have the most undifferentiated non-keratinizing cases (37.13%) and least Keratinizing squamous cell carcinoma (34.09%) compared with others. The Caucasians had most Keratinizing squamous cell type than the others (63.14%) and the least proportion of undifferentiated non-keratinizing cases (19.10%) ($p < 0.05$). In regard to the tumor grade level, the Caucasians had the most rate of well/moderately differentiated carcinoma (33.61%), and the Asians had the most occurrence of undifferentiated carcinoma (17.70%). These results were similar to the pattern of WHO classification.

The proportion of non-metastasis rate was 87.21% for Caucasians, and 83.67%, 88.83%, 87.45% for African Americans, Asians and Hispanics, respectively (Table 1.). The Asians had the most proportion (88.83%) of non-metastasis, and the African Americans had the most proportion of metastasis (16.33%) ($p < 0.05$).African Americans had the most proportion of neither operation nor radiation (15.22%), while Asians had the most proportion of radiotherapy with no operation (79.00%) and the least rate of operation plus radiotherapy (6.13%). The Hispanics had the most rate of operation with radiotherapy (13.53%).

3.2. Disparities of survival outcomes in different racial/ethnical groups

The unadjusted Kaplan–Meier model was used to estimate survival outcomes of the four major racial/ethnical groups in the United States.
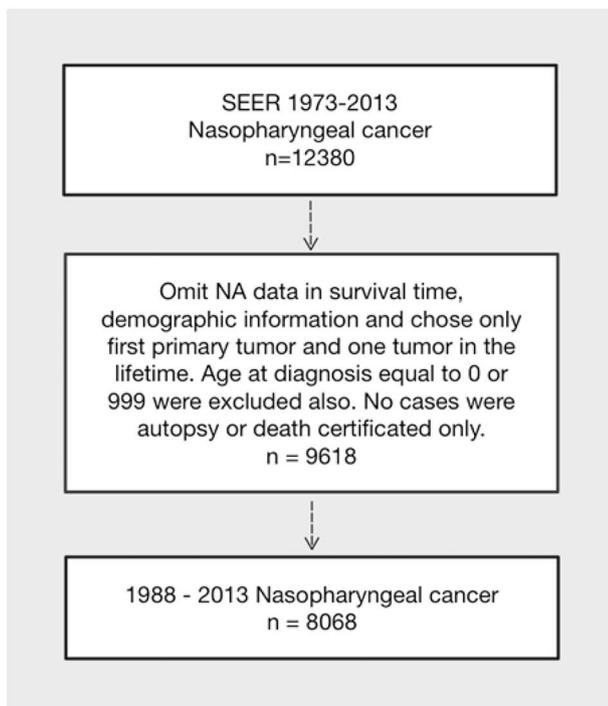
Table 1
Characteristics of different racial/ethical patients referred to NPC.

Variable	Caucasians	African Americans	Asians	Hispanics	P
Total, $N = 8068$	3283	915	3240	630	
Age at diagnosis, y					
Mean ± SD	56.60 ± 16.96	48.52 ± 18.40	51.25 ± 13.92	48.28 ± 18.70	0.83
Median (IQR)	58	50	50	50	
Age intervals					< 0.05
−40	469	265	717	198	
41–60	1396	414	1727	261	
61–70	769	129	490	101	
71–	649	107	306	70	
Sex, %(n)					0.78
Female	30.34(996)	28.96(265)	29.94(970)	31.27(197)	
Male	69.66(2287)	71.04(650)	70.06(2270)	68.73(433)	
Year at Diagnosis, % (n)					< 0.05
1988–1993	386	77	360	29	
1994–1998	362	92	515	66	
1999–2003	758	214	704	130	
2004–2008	893	267	796	182	
2009–2013	884	265	865	223	
Histology, % (n)					< 0.05
Keratinizing squamous	63.14(1547)	51.29(337)	34.09(763)	47.65(203)	
Differentiated non-keratinizing	17.76(435)	21.46(141)	28.78(644)	23.00(98)	
Undifferentiated non-keratinizing	19.10(468)	27.25(179)	37.13(831)	29.34(125)	
Unknown					
Tumor grade, %					< 0.05
Well or moderately differentiated	17.70(581)	12.79(117)	3.27(106)	10.48(66)	
Poorly differentiated	34.18(1122)	30.38(278)	35.34(1145)	32.22(203)	
Undifferentiated	18.03(592)	27.10(248)	33.61(1089)	25.71(162)	
Unknown	30.09(988)	29.73(272)	27.78(900)	31.59(199)	
Tumor size at diagnosis(mm), $n = 2222$	891	271	853	207	
Mean ± SD	41.70 ± 38.34	42.31 ± 18.38	36.43 ± 25.36	47.56 ± 67.46	0.69
Median (IQR)	39	40	34	41	
Lymph nodes, % (n)					0.69
No lymph node involvement	26.50(471)	22.93(122)	18.72(311)	20.00(81)	
Positive nodes	62.75(1115)	69.17(368)	72.91(1211)	66.67(270)	
Unknown or not applicable	10.75(191)	7.90(42)	8.37(139)	13.33(54)	
Extension					< 0.05
Non-Metastatic	87.21(2597)	83.67(702)	88.83(2655)	87.45(481)	
Metastatic	12.79(381)	16.33(137)	11.17(334)	12.55(69)	
Therapy					< 0.05
No radiation and surgery	14.47(380)	15.22(117)	10.02(250)	14.99(82)	
Radiation with no surgery	66.27(1741)	67.49(519)	79.00(1971)	65.45(358)	
Surgery with no radiation	2.89(76)	2.73(21)	0.80(20)	3.11(17)	
Surgery and radiation	12.18(320)	10.14(78)	6.13(153)	13.53(74)	
Unknown	4.19(110)	4.42(34)	4.05(101)	2.92(16)	

The results indicated that Asians showed a better overall survival than Caucasians, African Americans and Hispanics (Fig. 3A). However the overall survival analysis was conducted based on overall death, which included all causes of death. This may be not sufficient to reflect the clinical characteristics of NPC. On the account of this consideration, disease specific survival analysis was conducted, *i.e.* death due to NPC (SEER site recode: 20060) was considered as the event of interest, while death due to other causes was treated as the censoring event [6].The results revealed that racial/ethnical disparity disappeared between these four racial/ethnical groups (Fig. 3B).

The results were not in accord with Patel's study [6]. Their study concluded that African Americans and Asians with NPC had better disease specific survival compared with Caucasians. The reason was unclear, to clarify previous questions, the proportion of different causes of death was visualized as following mosaic plots (Fig. 4).

Mosaic plots in Fig. 4A indicated that the Asians had the lowest proportion of other cancer cause of death, but nearly the same proportion of NPC disease specific cause of death. However, the Caucasians have the most statistically significant proportion of cancer cause of death. These NPC cases selected in this study have merely one cancer registered in the database. However, some of them were caused to death due to other cites cancer. It may be explained that their death caused by the advance of the original cancer. Hence the cause-specific death may be more relevant to the NPC characteristics.

Consequently, the cause-specific of death due to NPC was investigated and the results indicated that Caucasians and African Americans had the most proportion of cause of death, while the Asians had the least proportion of cause-specific of death due to NPC (Fig. 4B).

Cause-specific survival analysis was conducted consequently. The results indicated that Asians had a survival advantage over Caucasians ($p < 0.001$) (Fig. 5). The African Americans showed marginal worsen survival outcome over Caucasians ($p = 0.005$), while Hispanics showed no survival benefit over Caucasians ($p = 0.26$). These results were in accordance with most existed publications [6,7].

3.3. Cox proportional hazards analysis of these four racial/ethnical groups

To further analyze the survival outcomes of these four racial/ethnical groups, unadjusted univariate and multivariate cox proportional hazards models were utilized. The sex, extension, therapy type, histology type and age at diagnosis were taken into consideration in the multivariate cox proportional hazards analysis (Table 2.). The Asians showed survival advantage over Caucasians in univariate (HR: 0.60, 95% CI: 0.55–0.64, $p < 0.001$) and multivariate analysis (HR: 0.81, 95% CI: 0.70–0.94, $p = 0.007$)(Fig. 6). African Americans showed no survival benefit over Caucasians, however the multivariate analysis showed marginal worsen survival prognosis against Caucasians (HR:
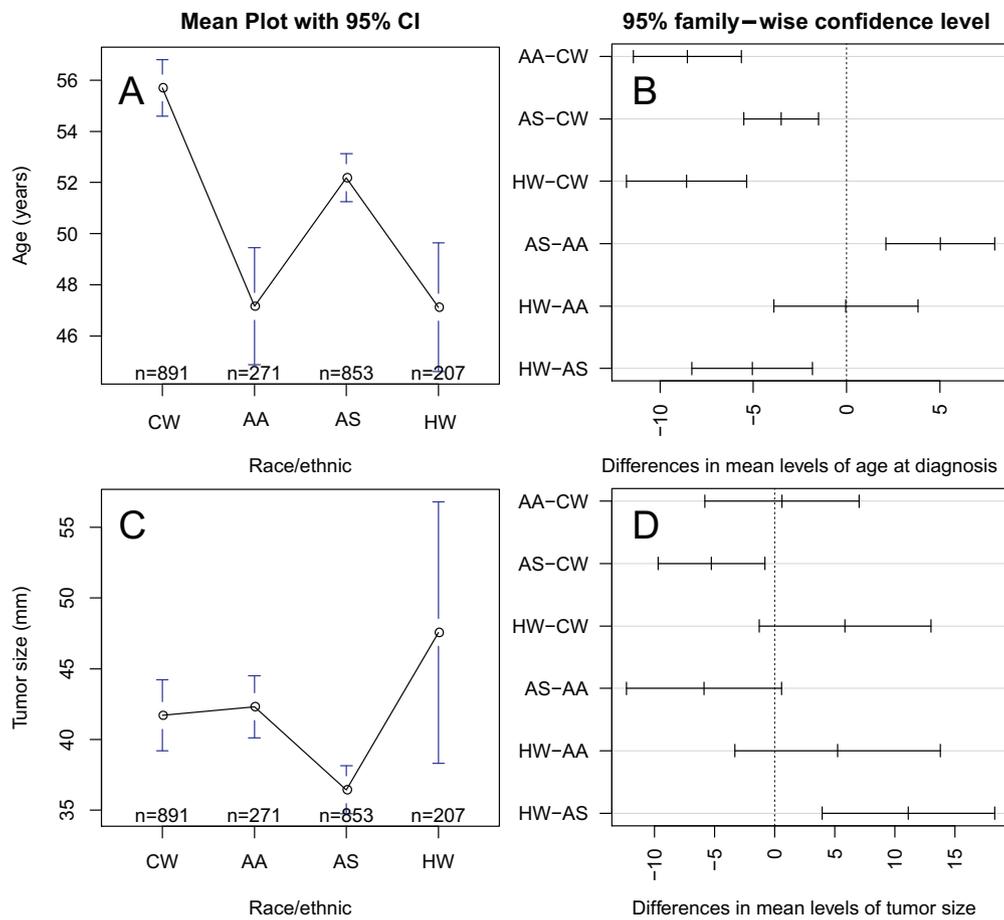
Fig. 2. (A, C) Mean and 95% CI of age and tumor size. (B, D) The family-wise confidence level of age and tumor size. CW Caucasian whites, AA African Americans, AS Asians, HW Hispanic Whites.
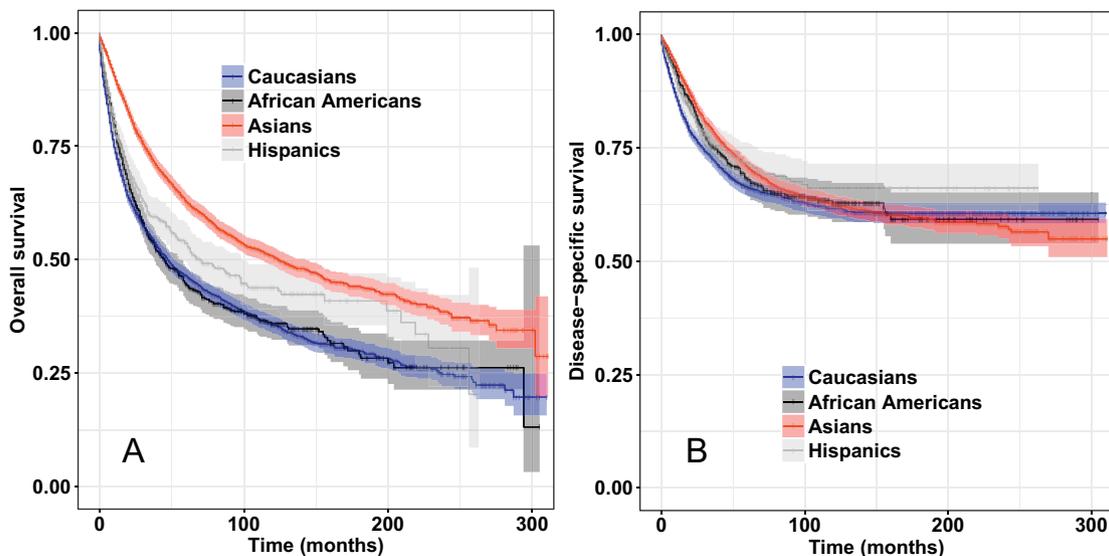

Fig. 3. Kaplan–Meier survival curves of different racial/ethnical groups. (A) Overall survival analysis of different racial/ethnical groups. (B) Disease specific survival of different racial/ethnical groups.

1.26, 95% CI: 1.07–1.49, $P < 0.005$).Hispanics showed marginal survival benefit over Caucasians in the univariate analysis (HR: 0.84, 95% CI: 0.73–0.96, $P = 0.011$), but turned out to be marginal worsen survival prognosis against Caucasians in multivariate analysis (HR: 1.27, 95% CI: 1.01–1.61, $P = 0.045$).

4. Discussion

4.1. The disparities in the four racial/ethnical groups

The Caucasians ($n = 3283$) and Asians ($n = 3240$) had the most populations of NPC, compared with 915 and 630 cases of African
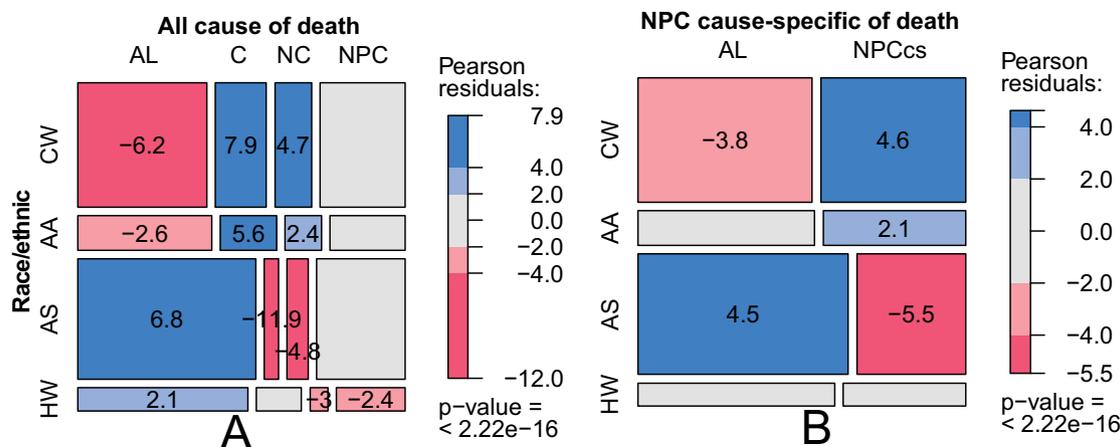
Fig. 4. (A) All cause of death. (B) NPC cause-specific of death. C:cancer-caused of death, NC: non-cancer cause of death, NPC: disease-specific cause of death. AL: alive or dead of other cause, NPCcs: cause-specific of death.
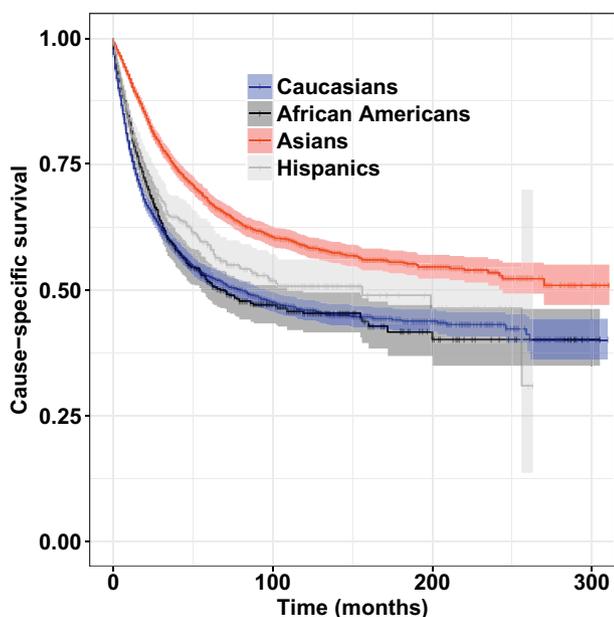

Fig. 5. Cause-specific survival curves of different racial/ethnical groups (P < 0.05).

Table 2
Multivariable cox regression modeling analysis on survival disparities of race/ethnicity.

	Univariate		Multivariate	
	HR (95% CI)	P trend	HR (95% CI)	P trend
Race/ethic				
Caucasians	Ref		Ref	
African Americans	0.97(0.87–1.09)	0.634	1.27(1.05–1.54)	0.014
Asians	0.60(0.55–0.64)	< 0.001	0.81(0.70–0.94)	0.007
Hispanics	0.84(0.73–0.96)	0.011	1.27(1.01–1.61)	0.045
Sex				
Female			Ref	
Male			0.99(0.86–1.13)	0.892
Age intervals				
≤ 40			Ref	
41–60			1.93(1.56–2.38)	< 0.001
61–70			2.37(1.87–3.00)	< 0.001
≥ 71			3.83(2.99–4.91)	< 0.001
Extension				
No metastasis			Ref	
Metastasis			1.71(1.51–1.94)	< 0.001
Histology				
Keratinizing squamous	Ref		Ref	
Differentiated non-keratinizing	0.58(0.53–0.65)	< 0.001	0.75(0.63–0.88)	< 0.001
Undifferentiated non-keratinizing	0.44(0.39–0.49)	< 0.001	0.66(0.53–0.82)	< 0.001
Tumor grade				
Well or moderately differentiated	Ref		Ref	
Poorly differentiated	0.63(0.56–0.70)	< 0.001	0.63(0.54–0.74)	< 0.001
Undifferentiated	0.41(0.37–0.47)	< 0.001	0.60(0.48–0.75)	< 0.001
Therapy				
No radiation and surgery	Ref		Ref	
Radiation with no surgery	0.33(0.31–0.37)	< 0.001	0.36(0.30–0.43)	< 0.001
Surgery with no radiation	0.32(0.23–0.44)	< 0.001	0.64(0.41–1.02)	0.062
Surgery plus radiation	0.23(0.19–0.27)	< 0.001	0.25(0.19–0.32)	< 0.001

Americans and Hispanics. The difference of age at diagnosis among these four racial/ethnical groups showed that Caucasians had more cases diagnosis at older age than Asians. Which may partially explained the worse survival outcomes of Caucasians than Asians [6]. The histology subtypes of these four racial/ethnical groups were statistically different. The Asians have the most undifferentiated non-keratinizing cases and least Keratinizing squamous cell carcinoma compared with others. The Caucasians had most Keratinizing squamous cell subtypes than other racial/ethnical groups and the least proportion of un-differentiated non-keratinizing cases. This may explain the disparity of better survival outcomes of Asians. Male had > 2 times to suffer from NPC than female, which imply the sex disparity regarding to the incidence of NPC. The imparity may due to the difference in life style patterns between male and female, nonetheless, this disparity not present in racial/ethnical.

The mean tumor size of Asians was slightly smaller than Caucasians and Hispanics. Lymph node involvement showed no statistical significance among these four racial/ethnical groups. However, the African Americans had a higher rate of metastasis at the time of diagnosis and the highest proportion of no treatment with the common

therapy of NPC(surgery or radiation). These may by reason of the minority racial groups had less access to and use of medical care in terms of clinic visits, screening, preventative care and diagnostic testing [13].
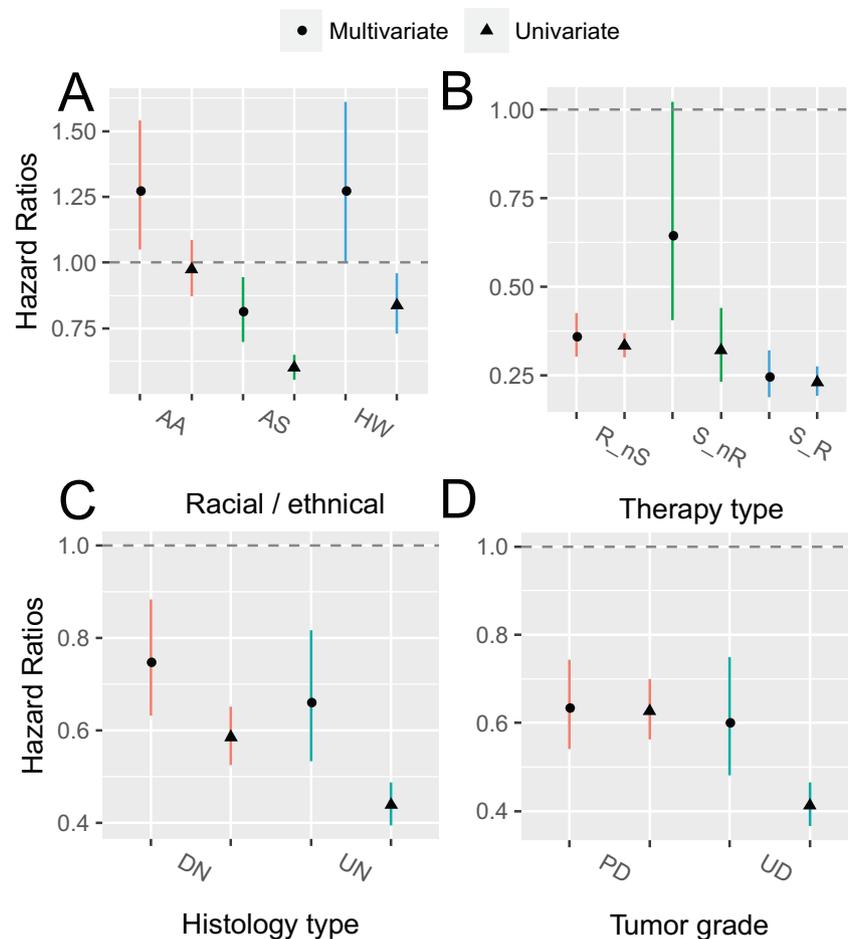
Fig. 6. The HRs of race/ethnicity (A), therapy(B), histology type(C) and tumor grade (D).

4.2. The different methods to compare survival times of these four racial/ethnical groups

The existed studies had two main conclusions about the racial/ethnical disparity between Asians and Caucasians. One is that Asians have survival advantage over Caucasian [7]; the other is that this advantage did not exist actually, though Patel et al. concluded that Asians showed survival advantage over Caucasians regarding to disease specific survival, but this advantage disappeared when considered the age at diagnosis [6,8]. However, the conclusion was drawn from different analysis protocol, which may put confounding factors to the results. The existed researches did not compare different protocols with the published methods. As a result, the comparison was conducted with the existing methods. The results indicated that the cause-specific of death maybe a better variants than disease specific death and overall death [6].

4.3. Racial/ethnical disparity referred to the survival of the NPC

This study indicated that Asians had a survival advantage over Caucasians and African Americans regarding to NPC. The African Americans showed marginal worsen survival results than Caucasians, and Hispanics had no survival benefit over Caucasians. After Cox proportional hazards analysis the survival benefit of Asian did not disappear, which suggested possible racial/ethnical disparity among Asians and Caucasians in the United States.

Though the Asians showed constant protective effect over Caucasians, the HR was smaller in scale than extension or not, histology type, therapy type or age at diagnosis (Fig. 6). Hence the existence of

obvious racial disparity was still in question. Thus, the racial/ethnical disparity may not be a strong independent prognostic factor. However the different distribution of histology type or grade level actually existed among Asians and Caucasians. This may come from genetic predispositions, viral agents, occupational exposures, and dietary exposures to chemical carcinogens [1,7,14].Epstein-Barr virus (EBV) is consistently detected in patients with nasopharyngeal carcinoma from regions of high and low incidence [1]. Buell analyzed mortality data of NPC patients in California offer strong evidence that off springs of US-born Chinese were at a lower risk of developing NPC [14].

4.4. Limitations

The SEER data base has a large population of NPC patients that can facilitate this multiracial study. However it lacking biological marker recordings, which were essential to the results, hence more studies should be conducted concerning the biological characteristics regarding NPC, which may reveal the underling mechanisms that facilitate targeted therapy.

5. Conclusion

Regarding NPC, Asians showed a cause-specific survival advantage over Caucasians, which was independent of sex, age at diagnosis, grade, TNM staging and treatment strategy. African Americans showed marginal worsen survival rates than Caucasians. Hispanics showed no survival advantage over Caucasians. Furthermore, when using overall survival and disease specific survival, the results were conflict. As a result, a properly chose model survival is essential.

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Declaration of competing interest

None.

Acknowledgements

References

[1] Wei WI, Sham JST. Nasopharyngeal carcinoma. Lancet 2005;365(June 11):2041–54.

[2] Hu J, et al. Use of radiation therapy in metastatic nasopharyngeal cancer improves survival: a SEER analysis. Sci Rep 2017;7(1):721.

[3] Kuan EC, et al. Nasopharyngeal adenocarcinoma: a population-based analysis. Am J Otolaryngol 2017;38(3):297–300.

[4] Han AY, et al. Epidemiology of nasopharyngeal lymphoma in the United States: a population-based analysis of 1119 cases. Otolaryngol Head Neck Surg 2017;156(5):870–6.

[5] Sun J, et al. Benefits of local tumor excision and pharyngectomy on the survival of nasopharyngeal carcinoma patients: a retrospective observational study based on SEER database. J Transl Med 2017;15(1):116.

[6] Patel VJ, Chen N, Resto VA. Racial and ethnic disparities in nasopharyngeal cancer survival in the United States: a SEER study. Otolaryngology–Head and Neck Surgery 2016;156(1):122–31.

[7] Wang Y, Zhang Y, Ma S. Racial differences in nasopharyngeal carcinoma in the United States. Cancer Epidemiol 2013;37(6):793–802.

[8] Bhattacharyya N. The impact of race on survival in nasopharyngeal carcinoma: a matched analysis. Am J Otolaryngol 2004;25(2):94–7.

[9] Sun LM, et al. Survival differences by race in nasopharyngeal carcinoma. Am J Epidemiol 2007;165(3):271–8.

[10] Ou SH, et al. Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. Ann Oncol 2007;18(1):29–35.

[11] Shavers VL, et al. Racial/ethnic patterns of care for cancers of the oral cavity, pharynx, larynx, sinuses, and salivary glands. Cancer Metastasis Rev 2003;22(1):25–38.

[12] Ning J, et al. Has racial difference in cause-specific death improved in older patients with late-stage breast cancer? Ann Oncol 2015;26(10):2161–8.

[13] Mayberry RM, Mili F, Ofili E. Racial and ethnic differences in access to medical care. Medical Care Research and Review: formerly Medical Care Review 2000;57(Suppl 1(suppl_1)). (p. 108).

[14] Buell P. The effect of migration on the risk of nasopharyngeal cancer among Chinese. Cancer Res 1974;34(5):1189–91.