

Changing Nasopharyngeal Carcinoma Survival in Southern China during 2000-2015: Results of a Retrospective Cohort Study

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Abstract

Objective: Around 50% of new nasopharyngeal carcinoma (NPC) cases come from China. The present study aimed to update the surveillance of NPC survival in southern China, and investigate the survival disparities between sexes within this patient population. **Methods:** Patients diagnosed with primary and invasive NPC between 2000 and 2015 were included in this study. Data on demographics, diagnosis, and follow-up to December 2020 were collected. Patients were stratified by diagnosis period, sex, and age at diagnosis. Survival analysis employed cohort and Life Table methods, Kaplan-Meier curves, log-rank tests, and Cox regression. **Results:** The study included 32,901 patients, of whom 69.6% were males. The overall 5-year survival rate rose from 69.6% in 2000-2003 to 83.3% in 2013-2015, with a consistent average increase of 3.3% every 3 years. For males, the 5-year survival rate increased from 66.3% to 82.0%, faster than females. Kaplan-Meier curves demonstrated a significantly higher survival rate for females than males, and subgroup analysis confirmed this advantage. The Cox proportional hazards model confirmed the lower mortality risk for females (HR 0.75, 95% CI: 0.71 - 0.78), patients with younger ages at diagnosis, and patients diagnosed in more recent years (All $P < 0.05$). **Conclusions:** The 5-year survival rate for NPC patients in southern China has significantly and steadily improved from 2000 to 2015, indicating the improved quality of cancer care in China. The survival advantage of female patients is not limited to younger patients but is also observed in postmenopausal patients, despite the gradual narrowing of the gender gap.

Keywords

Nasopharyngeal Carcinoma, Survival, Sex Difference, Southern China, Female, Prognosis

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1. Introduction

Nasopharyngeal carcinoma (NPC) is characterized by significant geographical and sex differences in its incidence and mortality rates worldwide, known to be prevalent in southern China and Southeast Asia, especially in Guangdong Province of China, with an incidence rate 20 times of the global average [1]-[4]. The latest data indicated that in 2022, there were 120,000 new NPC cases and 73,000 NPC-specific deaths worldwide, of which 43% and 38% were from China [1] [5]. The global incidence rate for NPC is recorded at 1.9 per 100,000 for males and 0.7 per 100,000 for females, with males being 2.7 times more susceptible to the condition than females [1].

Key risk factors for NPC include infection with the Epstein-Barr virus, genetic predisposition, specific human leukocyte antigen gene variants, immune status, the dietary habit of consuming salt-preserved fish, and a history of respiratory illnesses. Additional factors such as environmental agents, including consumption of nitrite-rich foods and preserved meats, may also contribute to the development of NPC [6]-[8]. In China, particularly in Guangdong Province, the high incidence of NPC may be closely related to local environmental conditions and lifestyle practices [3].

In response to this disease burden, China has implemented various measures over the past two decades to enhance early detection and treatment of NPC [9] [10]. These strategies involve establishing cancer screening programs in Guangdong and integrating advanced diagnostic and therapeutic approaches. These efforts have been instrumental in improving the short-term prognosis for NPC patients in China, manifested by a marked reduction in mortality rates [4] [11] [12]. However, available data on long-term trends of NPC survival in southern China are limited. This study leverages a substantial dataset to analyze the evolution of NPC survival rates from 2000 to 2015, and investigate the survival disparities between sexes within this patient population, providing further insight into the efficacy of cancer care initiatives in southern China.

2. Methods

2.1. Study Design and Participants

The study was designed as a retrospective cohort study, and conducted at a large-scale cancer center in Guangdong Province, South China. Referring to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), all patients with primary and invasive NPC patients newly diagnosed at the Cancer Center between January 2000 and December 2015 were included. Primarily, a total of 32,924 patients were included, of whom 23 were excluded for lack of follow-up data, resulting in a sample size of 32,901.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the cancer center. Informed consent was waived since only anonymous retrospective data were used.

2.2. Data Collection

Data on age at diagnosis, sex, time of diagnosis, and follow-up data to December 31, 2020 were collected from a prospectively maintained institutional database of the cancer center, which was previously compiled using information obtained from medical records and follow-up assessments.

All NPC patients who received treatment in the Cancer Center received regular follow-up investigations every 3 months during the first 3 years after treatment, every 6 months during the next 5 years, and annually after that. The raw follow-up data included the survival and health status of the patient, and the cause of death if the patient died before the investigation.

2.3. Statistical Analysis

Data were analyzed using SPSS software version 26 (IBM). Participants were categorized into five calendar periods (2000-2003, 2004-2006, 2007-2009, 2010-2012, and 2013-2015) according to time of diagnosis, and further stratified by both sex and age groups (<45 years as premenopausal, 45 - 54 years as perimenopausal, 55 - 64 years and ≥ 65 years as postmenopausal). Survival analysis was carried out using the cohort method, and the Life Table Method was employed to determine the overall 5-year survival rate. The Kaplan-Meier method was used to evaluate the survival probabilities of different NPC patient groups based on calendar periods and sex, with the log-rank test applied for comparisons. To assess the temporal trend in survival rates over the study period, a Weighted Least Squares Regression Model was utilized, and the improvement in survival was quantified as the absolute average change between successive calendar periods. Multivariate Cox proportional hazard modeling was performed to calculate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). A two-sided *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Study Population Characteristics

A total of 32,924 patients were initially diagnosed with primary invasive NPC at the Cancer Center from 2000 to 2015. Patients without follow-up data were excluded, resulting in a final cohort of 32,901 patients.

Table 1 summarizes the characteristics of the patients, revealing a male predominance (69.6%, $n = 22,894$) and a consistent age distribution across the five calendar periods. In the periods 2004-2006, 2007-2009, 2010-2012, and 2013-2015, the number of male patients was more than twice that of female patients, but this pattern was not observed in the 2000-2003 period (59.2% male vs. 40.8% female). Overall, nearly half (47.6%) of the patients were diagnosed before the age of 45, with another large proportion (29.9% and 16.7%) diagnosed at age 45 - 64. In essence, more than 90% of the patients were diagnosed with NPC before reaching 65 years of age, and only 5.7% of the patients were diagnosed at or after 65 years.

3.2. Trends in 5-Year Survival by Sex and Age Group

As shown in **Table 2**, consistent upward trends in 5-year survival rates were observed during the study period across the total patients and within both sexes (All *P* for trend <0.001). Overall, participants' 5-year survival rate improved from 69.6% (95% CI 68.5 - 70.6) in the 2000-2003 period to 83.3% (82.5 - 84.2) in the 2013-2015 period, with an average increase of 3.3% (2.6 - 4.0) every 3 years. Specifically, the survival rate for male patients increased from 66.3% (64.9 - 67.7) to 82.0% (81.0 - 83.1) over the observation period, with an average increase of 4.1% (3.4 - 4.8) every 3 years. For females, the rate increased from 74.4% (72.9 - 76.0) to 86.8% (85.3 - 88.4), with an average increase of 3.1% (2.2 - 4.0) every 3 years. During the observation period, female patients consistently exhibited higher survival rates across all five calendar periods, although the sex gap has been narrowing. In the 2000-2003 period, the survival rate disparity between sexes was 8.1% (74.4% for females vs. 66.3% for males), which decreased to 4.8% (86.8% for females vs. 82.0% for males) in the 2013-2015 period.

Table 1. Characteristics of study population (n = 32,901).

	Total (n = 32,901)	Calendar period [§]				
		2000-2003 (n = 8478)	2004-2006 (n = 5686)	2007-2009 (n = 4340)	2010-2012 (n = 6009)	2013-2015 (n = 8388)
Sex						
Male	22,894 (69.6)	5016 (59.2)	4009 (70.5)	3182 (73.3)	4516 (75.2)	6171 (73.6)
Female	10,007 (30.4)	3462 (40.8)	1677 (29.5)	1158 (26.7)	1493 (24.8)	2217 (26.4)
Age group, years						
<45	15,668 (47.6)	3905 (46.1)	2855 (50.2)	2153 (49.6)	2847 (47.4)	3908 (46.6)
45 - 54	9853 (29.9)	2667 (31.5)	1588 (27.9)	1262 (29.1)	1784 (29.7)	2552 (30.4)
55 - 64	5491 (16.7)	1349 (15.9)	902 (15.9)	694 (16.0)	1079 (18.0)	1467 (17.5)
≥65	1889 (5.7)	557 (6.6)	341 (6.0)	231 (5.3)	299 (5.0)	461 (5.5)

Data are N (%). [§]Participants were categorized into five calendar periods according to the year of NPC diagnosis, including 2000-2003, 2004-2006, 2007-2009, 2010-2012, and 2013-2015.

Table 2. Trends in 5-year survival[†] by sex and age group (n=32,901).

Variables	Calendar period [§]					Average change percalendar period	<i>P</i> for trend
	2000-2003	2004-2006	2007-2009	2010-2012	2013-2015		
Overall	69.6 (68.5 - 70.6)	72.0 (70.8 - 73.3)	76.9 (75.5 - 78.2)	79.3 (78.2 - 80.4)	83.3 (82.5 - 84.2)	3.3 (2.6 - 4.0)	<0.001*
Sex							
Male	66.3 (64.9 - 67.7)	69.2 (67.6 - 70.7)	74.8 (73.2 - 76.4)	77.8 (76.5 - 79.1)	82.0 (81.0 - 83.1)	4.1 (3.4 - 4.8)	<0.001*
Female	74.4 (72.9 - 76.0)	78.8 (76.7 - 80.8)	82.4 (80.1 - 84.7)	83.7 (81.8 - 85.7)	86.8 (85.3 - 88.4)	3.1 (2.2 - 4.0)	0.002*

Continued

Age group, years

<45	75.8 (74.3 - 77.2)	78.7 (77.1 - 80.3)	82.0 (80.3 - 83.7)	84.1 (82.6 - 85.5)	87.8 (86.7 - 89.0)	2.9 (2.4 - 3.4)	<0.001*
45 - 54	68.2 (66.3 - 70.2)	70.9 (68.5 - 73.3)	77.2 (74.7 - 79.6)	80.7 (78.7 - 82.6)	86.0 (84.5 - 87.5)	4.6 (3.9 - 5.2)	<0.001*
55 - 64	62.5 (59.7 - 65.3)	60.4 (56.9 - 63.8)	69.7 (66.1 - 73.3)	71.2 (68.4 - 74.1)	75.0 (72.5 - 77.5)	3.4 (0.6 - 6.2)	0.030*
≥65	48.8 (44.2 - 53.4)	51.4 (45.7 - 57.2)	47.9 (41.0 - 54.9)	54.4 (48.4 - 60.4)	56.1 (51.0 - 61.2)	1.7 (-0.4 - 3.7)	0.079

Data are % (95% Confidence Interval). †5-year survival rates were calculated using the Life Table Method. ‡Participants were categorized into five calendar periods according to the year of NPC diagnosis, including 2000-2003, 2004-2006, 2007-2009, 2010-2012, and 2013-2015. **P* for trend < 0.05, assessed by a Weighted Least Squares Regression Model, assuming a linear trend.

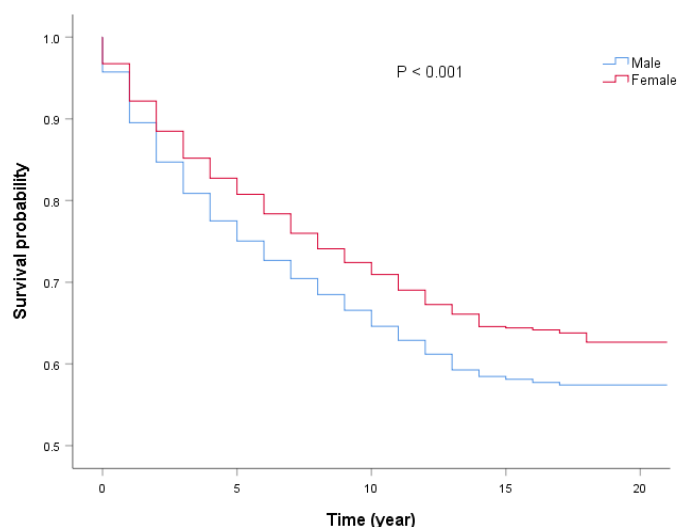
Comparisons across diagnostic age groups revealed that, overall, the 5-year survival rate decreased as the age at diagnosis increased (Table 2). From 2000-2015, three diagnostic age groups (<45, 45 - 54, and 55 - 64 years) demonstrated significant upward trends in 5-year survival rates. The most substantial increase was observed in the 45 - 54 years age group, with the 5-year survival rate climbing from 68.2% to 86.0%, representing an average increase of 4.6% every 3 years. In contrast, for the ≥65 years diagnostic age group, although there was an average increase of 1.7% in the survival rate every three years over the period, this upward trend was not statistically significant, and the survival rate remained around 50%.

3.3. 5-Year Survival Compared between Sexes

The Kaplan–Meier curves (Figure 1) and subgroup analysis (Table 3) revealed that female NPC patients had a significantly higher survival rate compared to males, particularly in younger age groups. Specifically, higher survival rates were found in female NPC patients in younger age groups (<45, 45 - 54, and 55 - 64 years) across all calendar periods (most *P* < 0.05), although this sex difference was not statistically significant in a few groups (e.g., patients aged <45 years in 2010-2012 and 2013-2015, and those aged 55 - 64 years in 2007-2009). For NPC patients diagnosed at 65 years or older, the survival advantage of female patients was observed only in the 2000-2003 and 2004-2006 periods (*P* < 0.05).

3.4. Multivariate Cox Regression Analysis of NPC Survival

The Cox proportional hazards model (Table 4) suggested that sex, diagnostic age, and the year of diagnosis were independently associated with NPC survival (All *P* < 0.001). Females exhibited a significantly lower risk of mortality than males, with an HR of 0.75 (95% CI: 0.71 - 0.78, *P* < 0.001). The survival rate significantly decreased as the diagnostic age increased. Compared to patients under 45 years old, those aged 45 - 54 years had an HR of 1.43, 55 - 64 years had an HR of 2.14, and ≥ 65 years had an HR of 3.45 (all *P* < 0.001). A significant improvement in NPC survival was observed across the calendar periods. Compared to the 2000-2003 period, the HRs for mortality were 0.86 (2004-2006), 0.68 (2007-2009), 0.59 (2010-2012), and 0.45 (2013-2015) for calendar periods (all *P* < 0.001).



$P < 0.001$ was assessed by the log-rank test, comparing between sexes

Figure 1. Kaplan–Meier curves for NPC patients by sex (n = 32,901).

Table 3. 5-year survival[†] compared between sexes by age groups (n=32,901).

Age groups	Calendar period [§]									
	2000-2003	<i>P</i> value	2004-2006	<i>P</i> value	2007-2009	<i>P</i> value	2010-2012	<i>P</i> value	2013-2015	<i>P</i> value
<45		<0.001		0.014		0.001		0.073		0.074
Male	73.3 (71.3 - 75.3)		77.3 (75.3 - 79.3)		80.2 (78.1 - 82.2)		83.1 (81.5 - 84.8)		87.1 (85.8 - 88.5)	
Female	79.2 (77.1 - 81.3)		81.7 (79.0 - 84.4)		86.4 (83.6 - 89.2)		86.6 (84.1 - 89.2)		89.5 (87.6 - 91.5)	
45 - 54		<0.001		<0.001		0.008		<0.001		<0.001
Male	65.1 (62.6 - 67.7)		66.3 (63.4 - 69.2)		75.1 (72.2 - 78.0)		78.6 (76.3 - 80.9)		84.5 (82.7 - 86.4)	
Female	73.0 (70.1 - 76.0)		82.8 (79.0 - 86.5)		83.7 (79.4 - 88.0)		87.0 (83.6 - 90.3)		90.1 (87.6 - 92.7)	
55 - 64		<0.001		0.001		0.169		0.015		0.039
Male	58.5 (54.9 - 62.1)		57.1 (53.0 - 61.2)		68.1 (63.9 - 72.3)		69.4 (66.0 - 72.7)		73.2 (70.3 - 76.2)	
Female	69.3 (64.9 - 73.7)		68.9 (62.7 - 75.0)		74.4 (67.5 - 81.3)		76.7 (71.4 - 82.0)		80.3 (75.7 - 84.8)	
≥65		<0.001		0.033		0.198		0.573		0.983
Male	44.5 (38.7 - 50.3)		49.0 (42.3 - 55.8)		44.0 (35.9 - 52.2)		54.6 (47.9 - 61.3)		55.3 (49.5 - 61.2)	
Female	55.9 (48.4 - 63.3)		57.6 (46.8 - 68.4)		57.8 (44.9 - 70.7)		53.4 (39.7 - 67.2)		59.0 (48.6 - 69.4)	

Data are % (95% Confidence Interval).[§]Participants were categorized into five calendar periods according to the year of NPC diagnosis, including 2000-2003, 2004-2006, 2007-2009, 2010-2012, and 2013-2015. [†]5-year survival rates were calculated using Life Table Method. ^{*}*P* value < 0.05, assessed by Wilcoxon (Gehan) Statistic, comparing between sexes.

Table 4. Multivariate Cox regression analysis of NPC survival.

	HR (95% CI)	P value
Sex		
Male	Ref	
Female	0.75 (0.71 - 0.78)	<0.001
Age group, years		
<45	Ref	
45 - 54	1.43 (1.35 - 1.50)	<0.001
55 - 64	2.14 (2.03 - 2.27)	<0.001
≥65	3.45 (3.22 - 3.71)	<0.001
Calendar period[§]		
2000-2003	Ref	
2004-2006	0.86 (0.81 - 0.91)	<0.001
2007-2009	0.68 (0.64 - 0.73)	<0.001
2010-2012	0.59 (0.55 - 0.62)	<0.001
2013-2015	0.45 (0.43 - 0.49)	<0.001

Cox proportional hazard models were used to estimate HR and 95% CI. [§]Participants were categorized into five calendar periods according to the year of NPC diagnosis, including 2000-2003, 2004-2006, 2007-2009, 2010-2012, and 2013-2015.

4. Discussion

NPC is characterized by a unique geographic distribution, rare in most parts of the world, but prevalent in southern China and southeast Asia, especially in Guangdong Province [1] [2] [5] [6] [13]. This study examined the demographic and survival outcomes of 32,901 NPC patients in Guangdong Province, revealing a substantial and consistent increase in survival rates from 2000 to 2015, and females at premenopausal (≤ 45 years), perimenopausal (46 - 54 years), and younger postmenopausal age (≥ 55 years) continue to exhibit more favorable prognoses.

In the current study, a significant increase in the 5-year survival rate for NPC patients in Guangdong is observed, rising from 69.6% for those diagnosed in 2000-2003 to 83.3% for those diagnosed in 2013-2015. A study analyzing data from 20,305 NPC patients in Guangdong from 1990 to 2012 reported a similar temporal trend [14]. Another study in Zhongshan City, Guangdong Province has reported a superior survival rate similar to ours, with an overall 5-year survival rate exceeding 80% [15], while several studies have reported significantly lower survival rates. For instance, a study in Sihui City, Guangdong Province, found that the five-year survival rate was 69.8% for NPC patients diagnosed between 2000-2005 [16], and another study based on 17 cancer registries in China reported an age-standardized 5-year survival rate as 45.5% for NPC patients diagnosed between 2012-2015 [17]. Potential reasons for the differences observed in survival rates across different studies might include variations in treatment

approaches, patient demographics, and study design. Besides, considering that the cancer center where we conducted this study is the largest institution for NPC diagnosis and treatment in southern China, equipped with the most advanced treatment equipment and protocols, our study has yielded a five-year survival rate relatively higher than some prior studies. Population-based cancer survival is a key indicator of the quality of cancer services, including early detection and appropriate management of cancer, people's access to and quality of cancer care, and funding of such services. It is likely that the substantial investment in health care by the Chinese government since 2003, has contributed to these survival improvements [9] [10].

5. Differences in Survival Rates by Sex

Men consist of the majority of NPC patients. Global cancer statistics reveal that males are at a 2.71-fold higher risk of developing NPC and a 3.00-fold increased risk of NPC-related mortality compared to females [1]. This study observed that overall, female patients consistently exhibited higher survival rates than their male counterparts throughout the observation period, and the Cox regression analysis also revealed a reduced mortality risk in female patients (HR 0.75, $P < 0.001$). Although this sex gap is gradually narrowing, as seen in the very slight difference in survival rates for NPC patients diagnosed between 2013 and 2015 (male 82.0% vs. female 86.8%), this difference remains statistically significant. This sex difference has been documented in numerous previous studies and can be attributed to several factors, including older age at diagnosis, more advanced disease stages, more aggressive tumor biology, suboptimal treatment outcomes, and increased engagement in risk behaviors such as smoking and alcohol consumption among males [18]-[23]. Additionally, sex hormones and sex chromosomes were reported to underlie the potential mechanisms contributing to the survival advantage observed in females [24] [25]. Under this context, some previous studies have categorized patients into three groups based on female menopausal status: premenopausal (≤ 45 years), perimenopausal (46 - 54 years), and postmenopausal groups (≥ 55 years). These studies concluded that the female survival advantage was only present in premenopausal and perimenopausal age groups. For the postmenopausal age group, females did not exhibit a survival advantage [18] [19] [21]. However, in this study, we observed that the female survival advantage still existed in some younger postmenopausal age patients (55 - 64 years) ($P < 0.05$). This suggests that, when analyzing the prognosis of NPC patients, it may be necessary to subdivide age groups more finely. Future research should also focus on this younger postmenopausal age group of NPC patients, analyzing the impact of sex hormones and other factors on their prognosis, and understanding the intrinsic and extrinsic reasons that differentiate this group from older postmenopausal patients (≥ 65 years).

As mentioned above, the sex gap in survival rates has been narrowing from 2000 to 2015, indicating that the improvement in survival rates for male patients is

occurring at a faster pace than for females, which may correlate with a trend towards younger ages at diagnosis among male individuals.

6. Differences in Survival Rates by Age

Our data imply that the prognosis for NPC patients improves with a younger age at diagnosis, and NPC patients diagnosed at or beyond the age of 65 exhibit a less favorable prognosis, with an overall 5-year survival rate of less than 50% and an increased mortality risk (HR 3.45, $P < 0.001$). This aligns with previous research, reporting that elderly NPC patients fare worse than younger patients, with 5-year survival rates between 43.9% and 61.8% [26]-[28]. This discrepancy may be attributed to a higher incidence of comorbidities, more advanced tumor stages, less effective treatment outcomes, a lack of adequate social support, decreased physiological resilience, and potential difficulties in accessing healthcare services in elderly patients. Noting the minimal difference in survival rates between patients under 45 years (75.8%) and those aged 45 - 54 years (68.2%), we suggest that even in the context of limited screening resources, efforts should be made to implement NPC screening before the age of 55 to enhance the likelihood of a favorable outcome and to increase survival rates. Early diagnosis and timely treatment will help reduce the burden of this cancer.

The study reconfirmed the survival advantage in female NPC patients and observed that the gender disparity is gradually narrowing over time. Designed as a retrospective analysis, the present study was insufficient to explore the underlying causes of this sex disparity. Moreover, the factors included in this study are limited. Incorporating variables such as tumor stage, clinical stage, and treatment modalities would allow for a more precise analysis of survival rate trends. Future work should incorporate a broader range of confounding factors, and focus on researching the mechanisms of sex differences in NPC progression and exploring the environmental and intrinsic reasons for the faster improvement in survival rates among male patients.

7. Conclusion

The 5-year survival rate for NPC patients in Guangdong Province has been significantly and steadily improving during 2000-2015, indicating the improved quality of cancer care in southern China. Despite the narrowing gender gap, female patients continue to exhibit a survival advantage, even in younger postmenopausal patients aged 55 - 64 years, highlighting the need for further research into gender-specific factors influencing prognosis and treatment outcomes.

Author Contributions

All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement

Patient consent was waived due to only anonymous retrospective data were used.

Data Availability Statement

The data presented in this study are available on request from the corresponding author due to privacy reasons.

Conflicts of Interest

The authors declare no conflicts of interest.

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