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Prognostic impact of family history in southern Chinese patients with undifferentiated nasopharyngeal carcinoma

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Background: Family history of cancer is associated with developing nasopharyngeal carcinoma (NPC); however, the impact of it on survival among established NPC patients remains unknown.

Methods: We retrospectively analysed 1773 southern Chinese patients. Associations between a first-degree family history of NPC and overall survival (OS), locoregional relapse-free survival (LRFS) and distant metastasis-free survival (DMFS) were estimated by Cox regression.

Results: Among 1773 patients, 207 (11.7%) reported a first-degree family history of NPC. Compared with patients without a family history, the adjusted hazard ratios among those with it were 0.60 (95% confidence interval (CI), 0.37–0.98; $P=0.040$) for OS, 0.52 (95% CI, 0.24–1.12; $P=0.096$) for LRFS and 0.51 (95% CI, 0.27–0.97; $P=0.040$) for DMFS. There were trends for improving OS, LRFS and DMFS with increasing number of affected relatives (P_{trend} : 0.050, 0.114 and 0.044, respectively). But no significant benefits of family history in second- or third-degree relatives were observed. In subgroup analysis, we observed the effects of family history with restriction to male patients and those of advanced stage and treated with conventional radiotherapy and addition of chemotherapy.

Conclusion: A first-degree family history of NPC is associated with improved survival of patients.

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that is especially prevalent in southern China. Despite improvements in the locoregional control rate due to the development of more precise imaging and radiotherapy (RT) and eradication of potential metastasis by chemotherapy, the survival of patients with advanced NPC remains unsatisfactory. Therefore, it is necessary to identify novel prognostic factors to recognise patients at high risk. As we know, Epstein–Barr virus (EBV) (Chien *et al*, 2001), southern Chinese tradition of consuming salted fish (Yu *et al*, 1986; Chang and Adami, 2006) and cigarette smoking (Xu *et al*, 2012) all play important roles in the aetiology. There is also substantial evidence for a heritable component in developing NPC based on segregation studies, linkage analysis and candidate

gene/genome-wide association studies (Feng *et al*, 2002; Hu *et al*, 2008; Bei *et al*, 2010). Importantly, family history of NPC has consistently been associated with an increased risk of developing the disease (Jia *et al*, 2004; Friberg *et al*, 2005; Jia *et al*, 2005; Yu *et al*, 2009). A large case–control study (Ren *et al*, 2010) even provided clear evidence that the risk of NPC was associated with a first-degree family history of cancers, including NPC and cancers of the head and neck, lung and breast. So it arouses a question – whether family history of NPC is associated with survival among patients with established NPC. Recently, the associations between family history and cancer survival have been studied in other cancers. Colon cancer (Chan *et al*, 2008; Zell *et al*, 2008) and gastric cancer (Han *et al*, 2012) patients with a first-degree family

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history showed a significant reduction in recurrence and death. Breast cancer patients with family history of breast cancer had a better prognosis as well (Malone *et al.*, 2011). However, the association of family history and NPC survival has not been explored up to now. Therefore, we performed this study to evaluate the effect of a first-degree family history of NPC on the clinicopathologic characteristics and survival of patients with NPC.

MATERIALS AND METHODS

Patient characteristics. The study was reviewed and approved by the Human Ethics Approval Committee at Sun Yat-sen University Cancer Center. Between January 2005 and May 2007, 2103 NPC patients who were hospitalised at the Sun Yat-sen University Cancer Center were potentially eligible for inclusion in this retrospective study. A total of 1773 patients were eventually included who (1) were newly diagnosed, biopsy-proven, non-metastatic NPC patients without previous anticancer treatment, (2) were at the age of 20 or > 20 years and born in southern China, (3) had a complete pretreatment evaluation including patient history, physical examination, haematology and biochemistry profiles, magnetic resonance imaging (MRI) of the nasopharynx and neck, chest radiography, abdominal sonography and a whole-body bone scan using single-photon emission computed tomography and (4) had a complete interview about family history, education and lifestyle behaviour.

Medical records were reviewed to extract data on basic characteristics including age, gender, education degree, cigarette smoking status at diagnosis (never/current/former smoker), alcohol drinking status at diagnosis (never/current/former drinker), pretreatment titre of serum immunoglobulin A against EBV viral capsid antigen (VCA-IgA), pathology (Shanmugaratnam and Sobin, 1991) and family history. Current smokers/drinkers were defined as patients who smoked/drank at diagnosis or had stopped for < 1 year. Former smokers/drinkers were patients who had stopped smoking or drinking for at least 1 year before treatment. All patients were restaged according to the seventh edition of the UICC/AJCC staging system (Edge *et al.*, 2009, 2010).

Treatment. All patients were treated by definitive RT. Details of the radiation techniques have been described previously (Ma *et al.*, 2007; Chen *et al.*, 2012). In addition, institutional guidelines recommended no chemotherapy for patients in stages I and II and induction, concurrent and adjuvant chemotherapy or combination treatment for those in stages III and IV. Induction or adjuvant chemotherapy consisted of cisplatin with 5-fluorouracil, cisplatin with taxoids or triplet of cisplatin and 5-fluorouracil plus taxoids every 3 weeks for two to three cycles. Concurrent chemotherapy consisted of cisplatin given on weeks 1, 4 and 7 of RT or cisplatin given weekly.

Family history assessment. Family history of cancer was ascertained by interviewing patients themselves and/or their family members at the time of case diagnosis. A positive family history was classified according to first degree, second degree or third degree. If the subjects had family history in several degrees of relatives, they were regarded as having a family history of closer degree in blood. We recorded the number of first-degree family members with NPC.

Follow-up. Patients were followed up every 3 months during the first 2 years and every 6 months thereafter until death. The assessments were performed by history and physical examination and nasopharyngoscopy at each follow-up visit. Local relapses were confirmed by biopsy, MRI scan or both. Regional relapses were diagnosed by clinical examination of the neck and, in doubtful cases, by fine-needle aspiration or an MRI scan of the neck. Distant

metastases were diagnosed by clinical symptoms, physical examinations and imaging methods including chest radiography, bone scan, MRI and abdominal sonography. Patients with relapse, distant metastasis or in persistent disease were delivered with salvage treatment including reirradiation, chemotherapy and surgery. The follow-up duration was calculated from the first day of therapy to either the day of death or the day of the last examination.

Study end points. Our primary end point was overall survival (OS), defined as the time from treatment to death resulting from any cause. Secondary end points were locoregional relapse-free survival (LRFS) and distant metastasis-free survival (DMFS), defined as the time from treatment to the first locoregional relapse and distant metastasis, respectively.

Statistical methods. All end points were examined using Kaplan–Meier methods and the log-rank test (Kaplan and Meier, 1958). Univariate stratified survival analyses were performed with hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate analyses were performed using the Cox proportional hazards model (Cox, 1972), adjusting for important prognostic factors. Comparisons of demographic, clinical and pathologic variables were performed using χ^2 statistic or Fisher's exact test for nominal variables as appropriate. Two-sided *P*-values < 0.05 were considered to be significant. All tests were conducted using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and clinicopathologic characteristics. A total of 1773 NPC patients were entered into this study (inclusion flow chart was presented in Supplementary Figure 1). Within a median follow-up duration of 71 months (range: 1–94 months) for the entire population and 74 months (range: 7–94 months) and 70 months (range: 1–94 months) for patients with and without a first-degree family history of NPC, 184/1773 (10.4%), 20/207 (9.7%) and 164/1566 (10.5%) patients were lost to follow up, respectively. Of these, 207/1773 (11.7%) patients had a family history of NPC in first-degree relatives and 52/1773 (2.9%) in second- and third-degree relatives. Fifteen of the 207 patients had both first- and second-/third-degree family history of NPC. Furthermore, 173/1773 (9.8%) patients had only one first-degree relative affected by NPC and 34/1773 (1.9%) had at least two affected first-degree family members.

The demographic and clinicopathologic characteristics of patients were compared according to with or without a first-degree family history of NPC (Table 1). There were no differences in the distributions of age group, gender, education degree, cigarette smoking status (never/current/former smoker), alcohol drinking status (never/current/former drinker), pretreatment titre of VCA-IgA ($\leq 1:160$ vs $> 1:160$), pathology (I/II/III) and radiation technique (all *P*-values ≥ 0.171).

Significant differences were observed in T stage, N stage, clinical stage and chemotherapy regimens. For patients with a first-degree family history of NPC, the proportion of advanced T stage, N stage and clinical stage was lower, and accordingly, the proportion of adding chemotherapy to RT was also lower than for those without a family history of NPC.

Effect of family history on survival. A first-degree family history of NPC was associated with a significant reduction in the risk of death (Figure 1). The 5-year OS rate was 92.6% for patients with a first-degree family history compared with 80.7% for those without such a profile (HR = 0.41, 95% CI, 0.26–0.65; *P* < 0.001). This remained unchanged after accounting for other important prognostic factors, including age group (categorical), gender,

Table 1. Demographic and clinicopathologic characteristics by with or without an FD-FH-NPC

Characteristics	With FD-FH-NPC (n = 207)		Without FD-FH-NPC (n = 1566)		P-value
	No.	%	No.	%	
Age group (years)					0.723
20–30	8	3.9	94	6.0	
31–40	62	30.0	424	27.1	
41–50	67	32.4	503	32.1	
51–60	47	22.7	363	23.2	
≥61	23	11.1	182	11.6	
Gender					0.171
Male	148	71.5	1188	75.9	
Female	59	28.5	378	24.1	
Education degree					0.237
Illiterate	11	5.3	84	5.4	
Primary	56	27.1	516	33.0	
Secondary	105	50.7	763	48.7	
Higher	35	16.9	203	13.0	
Smoking status ^a					0.806
Current smoker	77	37.2	619	39.5	
Former smoker	21	10.1	149	9.5	
Never smoker	109	52.7	798	51.0	
Drinking status ^a					0.766
Current drinker	24	11.6	207	13.2	
Former drinker	4	1.9	25	1.6	
Never drinker	179	86.5	1334	85.2	
VCA-IgA					0.495
≤1:160	107	51.7	770	49.2	
>1:160	100	48.3	796	50.8	
Pathology ^b					0.315 ^c
I	0	0	6	0.4	
II	7	3.4	86	5.5	
III	200	96.6	1474	94.1	
T stage					0.001
T1	36	17.4	205	13.1	
T2	72	34.8	398	25.4	
T3	70	33.8	589	37.6	
T4	29	14.0	374	23.9	
N stage					0.002
N0	50	24.2	263	16.8	
N1	124	59.9	883	56.4	
N2	29	14.0	377	24.1	
N3	4	1.9	43	2.7	
Clinical stage					<0.001
I	16	7.7	71	4.5	
II	76	36.7	396	25.3	
III	82	39.6	690	44.1	
IVa	29	14.0	366	23.4	
IVb	4	1.9	43	2.7	
Chemotherapy regimens					<0.001 ^c
None	70	33.8	357	22.8	
IC	27	13.0	412	26.3	
CCRT	69	33.3	429	27.4	
IC + CCRT	33	15.9	292	18.6	
CCRT + AC	5	2.4	58	3.7	
IC + CCRT + AC	3	1.4	18	1.1	

Table 1. (Continued)

Characteristics	With FD-FH-NPC (n = 207)		Without FD-FH-NPC (n = 1566)		P-value
	No.	%	No.	%	
Radiation technique					0.943 ^c
IMRT	49	23.7	375	23.9	
3DCRT	5	2.4	31	2.0	
Conventional	153	73.9	1160	74.1	

Abbreviations: AC = adjuvant chemotherapy; CCRT = concurrent chemoradiotherapy; FD-FH-NPC = first-degree family history of nasopharyngeal carcinoma; IC = induction chemotherapy; IMRT = intensity-modulated radiotherapy; VCA-IgA = immunoglobulin A against Epstein-Barr virus viral capsid antigen; WHO = World Health Organization; 3DCRT = three-dimensional conformal radiotherapy.

^aCurrent smokers/drinkers are defined as patients who smoke/drink at diagnosis or have stopped for <1 year. Former smokers/drinkers are patients who have stopped smoking or drinking for at least 1 year before treatment.

^bBased on the criteria of WHO histological type (1991): I = squamous cell carcinomas; II = differentiated non-keratinising carcinoma; III = undifferentiated non-keratinising carcinoma.

^cP-values by Fisher's exact probability test and all others by Pearson's χ^2 test.

education degree (categorical), smoking status (never/current/former smoker), drinking status (never/current/former drinker), titre of VCA-IgA ($\leq 1:160$ vs $> 1:160$), pathology (I/II/III), T stage (T1/T2/T3/T4), N stage (N0/N1/N2/N3), chemotherapy regimens and radiation technique. Compared with patients without a first-degree family history, those with a family history of NPC had a multivariate HR of 0.60 (95% CI, 0.37–0.98; $P = 0.040$) for death (Table 2). Furthermore, the results for the risk of locoregional relapse and distant metastasis were quite similar to those for death. In univariate analysis, a first-degree family history of NPC was associated with improved LRFS (unadjusted HR = 0.51, 95% CI, 0.28–0.95; $P = 0.033$) and DMFS (unadjusted HR = 0.43, 95% CI, 0.25–0.75; $P = 0.003$) (Figure 1). In multivariate analyses, adjusted HRs for LRFS and DMFS were 0.52 (95% CI, 0.24–1.12; $P = 0.096$) and 0.51 (95% CI, 0.27–0.97; $P = 0.040$) (Table 2).

To specify the influence of family history on survival, we conducted second analyses (Table 2). First, compared with patients without a first-degree family history of NPC, those with one affected relative had a multivariate HR of 0.61 (95% CI, 0.36–1.02; $P = 0.059$) for OS, 0.52 (95% CI, 0.23–1.18; $P = 0.118$) for LRFS and 0.53 (95% CI, 0.27–1.03; $P = 0.062$) for DMFS. For participants with two or more affected first-degree relatives, we observed a multivariate HR of 0.57 (95% CI, 0.14–2.28; $P = 0.423$) for OS, 0.54 (95% CI, 0.07–3.88; $P = 0.538$) for LRFS and 0.41 (95% CI, 0.06–2.91; $P = 0.369$) for DMFS. So there was a trend for reduction of overall mortality, locoregional relapse and distant metastasis with an increasing number of affected family members (P -values for trend were 0.050, 0.114 and 0.044, respectively). Second, compared with patients without a second- or third-degree family history of NPC, those with such a profile had a multivariate HR of 0.92 (95% CI, 0.41–2.08; $P = 0.841$) for OS, 0.61 (95% CI, 0.15–2.47; $P = 0.486$) for LRFS and 0.39 (95% CI, 0.10–1.58; $P = 0.186$) for DMFS. Hence, second- and third-degree family history of NPC was not significantly associated with survival. Finally, we further addressed the concern that patients with a family history of NPC might have a different prognosis related to earlier detection of their cancers. Among stage III and IV patients, we observed a multivariate HR of 0.57 (95% CI, 0.34–0.95; $P = 0.033$) for OS, 0.54 (95% CI, 0.24–1.23; $P = 0.143$) for LRFS and 0.49 (95% CI, 0.25–0.96; $P = 0.036$) for DMFS when comparing patients with or without a first-degree family history of NPC. These results were quite similar to those for the entire

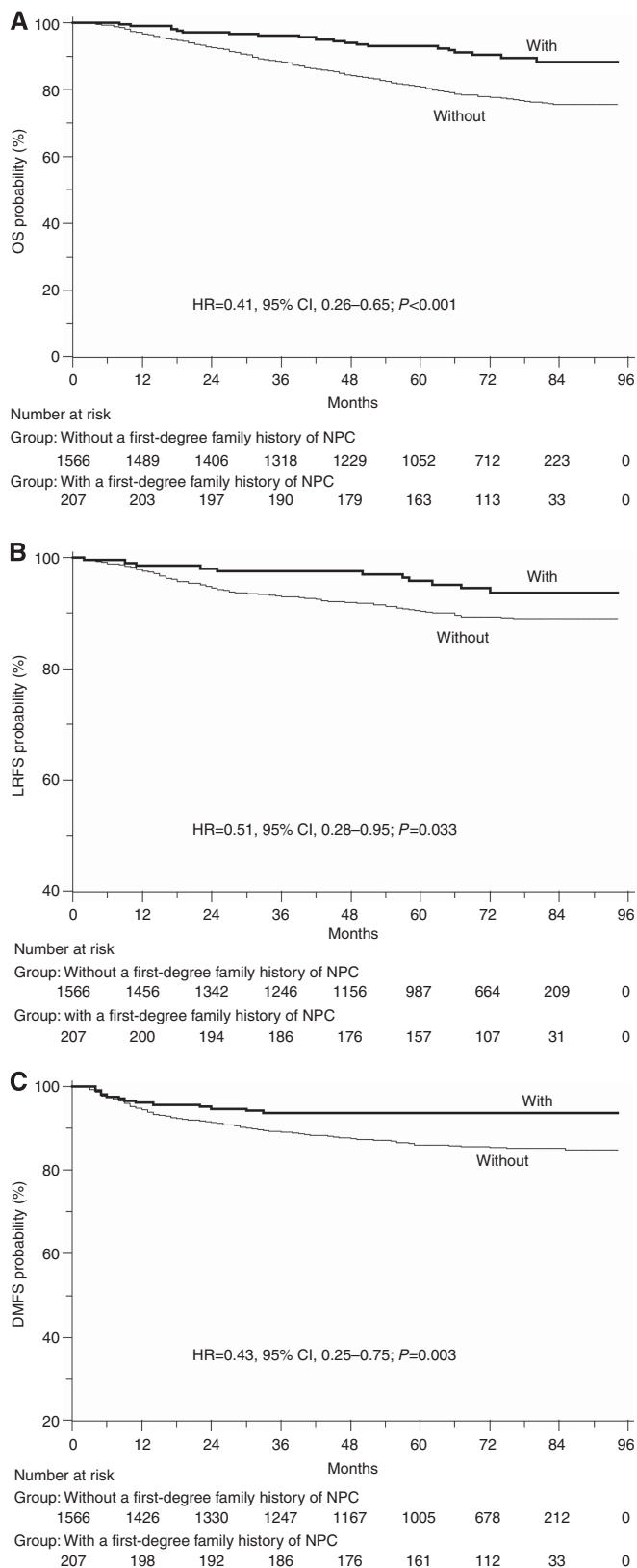


Figure 1. (A) OS, (B) LRFS and (C) DMFS curves of patients with and without a first-degree family history of NPC.

population. Among stage I and II patients, the adjusted HRs for OS, LRFS and DMFS were 0.31 (95% CI, 0.07–1.34; P=0.117), 0.39 (95% CI, 0.05–2.99; P=0.364) and 0.31 (95% CI, 0.04–2.35; P=0.257), respectively. The OS curves of patients in stages I plus

II, III and IV with or without a first-degree family history of NPC were presented in Supplementary Figure 2.

In addition, we also assessed the association between a first-degree family history of NPC and OS across strata of other potential predictors of patient outcome (Table 3). The effect of family history on the risk of death was not significantly modified by age, education degree, smoking and drinking status or titre of VCA-IgA. However, the benefit of family history in decreasing risk of death was restricted to male patients (adjusted HR = 0.55, 95% CI, 0.30–0.98; P = 0.043). Moreover, a family history of NPC had significant association with OS among patients treated with addition of chemotherapy to RT and with conventional radiation technique (adjusted HR = 0.57, 95% CI, 0.34–0.95, P = 0.033 and adjusted HR = 0.55, 95% CI, 0.31–0.96, P = 0.037, respectively).

DISCUSSION

Several studies have demonstrated that family history of NPC increased the risk of developing NPC (Jia *et al*, 2004; Friberg *et al*, 2005; Jia *et al*, 2005; Yu *et al*, 2009). However, to date, no studies have examined the influence of family history of NPC on subsequent outcomes in patients with established cancer. This study included 1773 NPC patients, among which 207 (11.7%) had a family history of NPC in first-degree relatives. We demonstrated that a first-degree family history of NPC was associated with a significant reduction in risk of death, locoregional relapse and distant metastasis, and it remained unchanged after adjusting for known prognostic factors. Our findings were quite similar to previous studies in colorectal cancer (Zell *et al*, 2008; Morris *et al*, 2013), colon cancer (Chan *et al*, 2008), gastric cancer (Han *et al*, 2012) and breast cancer (Malone *et al*, 2011).

We then examined the effects according to the number of affected first-degree family members; resultantly, a significant trend for improvement in DMFS and OS with an increasing number of first-degree family members was observed. Whereas in second- or third-degree relatives, the effects of family history were not observed, which were consistent with reports in gastric cancer (Han *et al*, 2012) and breast cancer (Malone *et al*, 1996, 2011). Further investigations are required because this nonsignificant differential survival seemed to be driven by the small sample size of cases with a second- or third-degree family history of NPC. Additionally, we performed stratified analysis according to clinical stage and found significant effects of family history only in locoregionally advanced stage patients. This may mainly result from a large number of patients and high event rates in the advanced clinical stage stratum; the interactions between clinical stage and a first-degree family history of NPC (P < 0.001) may also contribute to it. Individuals with a family history of the disease in first-degree relatives might be more likely to undergo regular NPC surveillance, such as Epstein–Barr virus antibodies and DNA copies, and had relatively early clinical stage as shown in Table 1. Despite of adjusting for smoking status and other prognostic factors, we found that the effects of family history were restricted to male patients. A recent study (Lu *et al*, 2013) revealed that the female sex was positively associated with an early T stage, N stage and clinical stage; reduced disease progression and cancer-related deaths and was a favourable independent prognostic factor. This suggested that some intrinsic features of the female sex should interact and confound the effects of family history. But we detected no interactions between gender and a first-degree family history of NPC (P = 0.366). Therefore, the significant differences of the effects of a first-degree family history in male and female patients seem to be true if the influence of small sample size in male stratum is excluded. Moreover, we found that the effect of family history was restricted in patients treated with addition of

Table 2. Multivariate analysis for OS, LRFS and DMFS^a

	OS				LRFS			DMFS		
	No. at risk	No. of events	aHR (95% CI)	P-value	No. of events	aHR (95% CI)	P-value	No. of events	aHR (95% CI)	P-value
FD-FH-NPC										
Without	1566	338	1.00		148	1.00		213	1.00	
With	207	20	0.60 (0.37–0.98)	0.040	11	0.52 (0.24–1.12)	0.096	13	0.51 (0.27–0.97)	0.040
A second- or third-degree family history of NPC										
No	1721	352	1.00		157	1.00		224	1.00	
Yes	52	6	0.92 (0.41–2.08)	0.841	2	0.61 (0.15–2.47)	0.486	2	0.39 (0.10–1.58)	0.186
Number of first-degree relatives with NPC										
0	1566	338	1.00		148	1.00		213	1.00	
1	173	17	0.61 (0.36–1.02)	0.059	9	0.52 (0.23–1.18)	0.118	11	0.53 (0.27–1.03)	0.062
≥2	34	3	0.57 (0.14–2.28)	0.423	2	0.54 (0.07–3.88)	0.538	2	0.41 (0.06–2.91)	0.369
FD-FH-NPC in stage I and II patients										
Without	467	43	1.00		31	1.00		22	1.00	
With	92	3	0.31 (0.07–1.34)	0.117	4	0.39 (0.05–2.99)	0.364	2	0.31 (0.04–2.35)	0.257
FD-FH-NPC in stage III and IV patients										
Without	1099	295	1.00		117	1.00		191	1.00	
With	115	17	0.57 (0.34–0.95)	0.033	7	0.54 (0.24–1.23)	0.143	11	0.49 (0.25–0.96)	0.036

Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; DMFS = distant metastasis-free survival; FD-FH-NPC = first-degree family history of nasopharyngeal carcinoma; LRFS = locoregional relapse-free survival; NPC = nasopharyngeal carcinoma; OS = overall survival.

^aMultivariate HRs and 95% CIs are adjusted for age group (categorical), gender, education degree (categorical), smoking status (never/current/former smoker), drinking status (never/current/former drinker), pathology (I/II/III), T stage (T1/T2/T3/T4), N stage (N0/N1/N2/N3), titre of VCA-IgA (≤ 1:160 vs > 1:160), chemotherapy regimens and radiation technique.

chemotherapy to RT. Unfortunately, there were significant interactions between chemotherapy (yes/no) and a first-degree family history of NPC ($P = 0.046$). As shown in Table 1, patients with a family history of NPC had an obvious higher proportion of RT alone treatment than patients without a family history of NPC. So it remains uncertain whether the favourable prognostic value of family history is applicable to patients with RT alone. Finally, the effect of family history was observed only in patients treated with conventional radiation technique, and no interaction between radiation technique and a first-degree family history of NPC was showed ($P = 0.553$) when we include an interaction term in the model. This differentiation was mainly due to a higher proportion of advanced stage patients among this group than those treated with intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3DCRT). Meanwhile, there were low proportion of patients treated with IMRT/3DCRT and a few events in the group of positive family history. This may partially explain no effects of family history in patients treated with IMRT/3DCRT.

A major limitation of our study is that we relied on self-reported family history and might possibly misclassify family history status, especially under-reporting the second-degree family history. But prior studies have demonstrated such data to be reliable (Aitken *et al*, 1995; Kerber and Slattery, 1997). Another limitation is that we could not collect information on the age at which the first-degree relative was diagnosed with NPC, as the effect of family history might be different according to it. The third concern was that we failed to include data regarding pretreatment plasma EBV DNA concentrations, which had been demonstrated to strongly predict survival of NPC (Lo *et al*, 2000; Lin *et al*, 2004). However, we performed stratified analysis according to pretreatment serum

EBV VCA-IgA antibody, another significant prognostic factor for survival (Ling *et al*, 2009), albeit DNA concentrations seemed to be superior to it in prognostic predictions for NPC (Tsu *et al*, 2007). Studies based on EBV DNA concentrations are being planned. Moreover, the chemotherapy regimens were not totally identified with the latest NCCN guideline for different criteria of staging systems and development of treatment regimen. During the period when patients were treated, many patients were encouraged to participate in randomised trials, which also resulted in heterogeneous treatment strategies. But we conducted multivariate analyses accounting for RT technique and chemotherapy regimens. Additionally, the smoking and drinking status questionnaire was not administered during follow-up; we were unable to fully adjust for the confounding effects by smoking and drinking status at diagnosis alone. But to date, no studies have demonstrated the role of cigarette smoking or alcohol intake during or after treatment in affecting survival of NPC. In this study, we accounted for socioeconomic status by education degree alone; this limitation cannot be neglected as well. We are planning to detect the prognostic value of pretreatment body mass index – another factor partially representing socioeconomic status.

More importantly, it is not clear why a first-degree family history of NPC affects survival of patients. Our study showed more early-stage patients among those with a family history of NPC, which strongly supports an assumption of surveillance monitoring for individuals with a family history of NPC. Health-related behaviour may also explain our observations, as found in gastric cancer (Han *et al*, 2012). Yet we here did not observe significant differences in the proportion of smokers or drinkers in patients with or without a family history of NPC. Underlying molecular and pathogenic differences might play an intrinsic role in the effect

Table 3. Subgroup analysis of OS by patients' characteristics in terms of with or without an FD-FH-NPC

Factor	Five-year OS rate (%)	P for OS by each factor	No. of events/No. at risk		aHR (95% CI) ^a	P for OS between with and without FD-FH-NPC
			Without FD-FH-NPC	With FD-FH-NPC		
Overall	82.2		338/1566	20/207	0.60 (0.37–0.98)	0.040
Age (years)		<0.001				
≤53	86.3		197/1159	12/158	0.67 (0.37–1.21)	0.187
>53	70.1		141/407	8/49	0.50 (0.20–1.23)	0.131
Gender		0.005				
Male	80.5		276/1188	12/148	0.55 (0.30–0.98)	0.043
Female	87.2		62/378	8/59	0.83 (0.33–2.10)	0.690
Education		<0.001				
Illiterate and primary	77.3		163/600	9/67	0.48 (0.21–1.09)	0.079
Secondary and higher	85.1		175/966	11/140	0.72 (0.39–1.35)	0.306
Smoking status		<0.001				
Yes	76.2		219/768	15/98	0.74 (0.41–1.34)	0.324
No	87.9		119/798	5/109	0.41 (0.17–1.02)	0.056
Drinking status		0.056				
Yes	78.5		61/232	3/28	0.53 (0.13–2.26)	0.393
No	82.8		277/1334	17/179	0.65 (0.39–1.11)	0.112
VCA-IgA		0.011				
≤1:160	84.5		148/770	8/107	0.45 (0.18–1.10)	0.081
>1:160	79.9		190/796	12/100	0.73 (0.40–1.32)	0.294
Clinical stage		<0.001				
I + II	92.9		43/467	3/92	0.31 (0.07–1.34)	0.117
III + IV	77.1		295/1099	17/115	0.57 (0.34–0.95)	0.033
Chemotherapy		<0.001				
Yes	80.1		280/1209	16/136	0.57 (0.34–0.95)	0.030
No	88.6		58/357	4/71	0.51 (0.18–1.45)	0.203
Radiation technique		0.003				
IMRT/3DCRT	86.9		63/406	5/54	0.79 (0.28–2.23)	0.656
Conventional	80.5		275/1160	15/153	0.55 (0.31–0.96)	0.037

Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; FD-FH-NPC = first-degree family history of nasopharyngeal carcinoma; IMRT = intensity-modulated radiotherapy; OS = overall survival; VCA-IgA = immunoglobulin A against Epstein-Barr virus viral capsid antigen; 3DCRT = three-dimensional conformal radiotherapy.

^aMultivariate HRs and 95% CIs are adjusted for age group (categorical), gender, education degree (categorical), smoking status (never/current/former smoker), drinking status (never/current/former drinker), pathology (I/II/III), T stage (T1/T2/T3/T4), N stage (N0/N1/N2/N3), titre of VCA-IgA (≤1:160 vs >1:160), chemotherapy regimens and radiation technique.

of family history, although we observed no significantly different distribution of VCA-IgA and pathology in patients with and without a family history of NPC. Further basic researches into genetic differences were needed to fully elucidate the potential mechanisms.

To summarise, this study, as the first one, showed better survival for patients who had a first-degree family history of NPC than for patients without this profile. Further studies are needed to explore the biological, genetic or behavioural differences in NPC according to the presence of family history.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Aitken J, Bain C, Ward M, Siskind V, MacLennan R (1995) How accurate is self-reported family history of colorectal cancer? *Am J Epidemiol* **141**(9): 863–871.

Bei JX, Li Y, Jia WH, Feng BJ, Zhou G, Chen LZ, Feng QS, Low HQ, Zhang H, He F, Tai ES, Kang T, Liu ET, Liu J, Zeng YX (2010) A genome-wide association study of nasopharyngeal carcinoma identifies three new susceptibility loci. *Nat Genet* **42**(7): 599–603.

Chan JA, Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Thomas J, Schaefer P, Whittom R, Hantel A, Goldberg RM, Warren RS, Bertagnolli M, Fuchs CS (2008) Association of family history with cancer recurrence and survival among patients with stage III colon cancer. *JAMA* **299**(21): 2515–2523.

- Chang ET, Adami HO (2006) The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* **15**(10): 1765–1777.
- Chen L, Mao Y-P, Xie F-Y, Liu L-Z, Sun Y, Tian L, Tang L-L, Lin A-H, Li L, Ma J (2012) The seventh edition of the UICC/AJCC staging system for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic area in China. *Radiother Oncol* **104**(3): 331–337.
- Chien YC, Chen JY, Liu MY, Yang HI, Hsu MM, Chen CJ, Yang CS (2001) Serologic markers of Epstein–Barr virus infection and nasopharyngeal carcinoma in Taiwanese men. *N Engl J Med* **345**(26): 1877–1882.
- Cox DR (1972) Regression models and life tables. *J R Stat Soc B* **34**: 187–220.
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (2009) *AJCC Cancer Staging Manual*. 7th edn. (Springer: New York).
- Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (2010) *AJCC Cancer Staging Handbook from the AJCC Cancer Staging Manual*. 7th edn. (Springer: New York).
- Feng BJ, Huang W, Shugart YY, Lee MK, Zhang F, Xia JC, Wang HY, Huang TB, Jian SW, Huang P, Feng QS, Huang LX, Yu XJ, Li D, Chen LZ, Jia WH, Fang Y, Huang HM, Zhu JL, Liu XM, Zhao Y, Liu WQ, Deng MQ, Hu WH, Wu SX, Mo HY, Hong MF, King MC, Chen Z, Zeng YX (2002) Genome-wide scan for familial nasopharyngeal carcinoma reveals evidence of linkage to chromosome 4. *Nat Genet* **31**(4): 395–399.
- Friborg J, Wohlfahrt J, Koch A, Storm H, Olsen OR, Melbye M (2005) Cancer susceptibility in nasopharyngeal carcinoma families – a population-based cohort study. *Cancer Res* **65**(18): 8567–8572.
- Han MA, Oh MG, Choi IJ, Park SR, Ryu KW, Nam BH, Cho SJ, Kim CG, Lee JH, Kim YW (2012) Association of family history with cancer recurrence and survival in patients with gastric cancer. *J Clin Oncol* **30**(7): 701–708.
- Hu LF, Qiu QH, Fu SM, Sun D, Magnusson K, He B, Lindblom A, Ernberg I (2008) A genome-wide scan suggests a susceptibility locus on 5p 13 for nasopharyngeal carcinoma. *Eur J Hum Genet* **16**(3): 343–349.
- Jia WH, Collins A, Zeng YX, Feng BJ, Yu XJ, Huang LX, Feng QS, Huang P, Yao MH, Shugart YY (2005) Complex segregation analysis of nasopharyngeal carcinoma in Guangdong, China: evidence for a multifactorial mode of inheritance (complex segregation analysis of NPC in China). *Eur J Hum Genet* **13**(2): 248–252.
- Jia WH, Feng BJ, Xu ZL, Zhang XS, Huang P, Huang LX, Yu XJ, Feng QS, Yao MH, Shugart YY, Zeng YX (2004) Familial risk and clustering of nasopharyngeal carcinoma in Guangdong, China. *Cancer* **101**(2): 363–369.
- Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observation. *J Am Stat Assoc* **53**: 457–481.
- Kerber RA, Slattery ML (1997) Comparison of self-reported and database-linked family history of cancer data in a case–control study. *Am J Epidemiol* **146**(3): 244–248.
- Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, Jiang RS (2004) Quantification of plasma Epstein–Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med* **350**(24): 2461–2470.
- Ling W, Cao SM, Huang QH, Li YH, Deng MQ (2009) Prognostic implication of pretreatment titer of serum immunoglobulin A against Epstein–Barr virus capsid antigen in nasopharyngeal carcinoma patients in Sihui, Guangdong. *Ai Zheng* **28**(1): 57–59.
- Lo YM, Chan AT, Chan LY, Leung SF, Lam CW, Huang DP, Johnson PJ (2000) Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein–Barr virus DNA. *Cancer Res* **60**(24): 6878–6881.
- Lu X, Wang FL, Guo X, Wang L, Zhang HB, Xia WX, Li SW, Li NW, Qian CN, Xiang YQ (2013) Favorable prognosis of female patients with nasopharyngeal carcinoma. *Chin J Cancer* **32**(5): 283–288.
- Ma J, Liu L, Tang L, Zong J, Lin A, Lu T, Cui N, Cui C, Li L (2007) Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: prognostic value and staging categories. *Clin Cancer Res* **13**(5): 1445–1452.
- Malone KE, Daling JR, Doody DR, O'Brien C, Resler A, Ostrander EA, Porter PL (2011) Family history of breast cancer in relation to tumor characteristics and mortality in a population-based study of young women with invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* **20**(12): 2560–2571.
- Malone KE, Daling JR, Weiss NS, McKnight B, White E, Voigt LF (1996) Family history and survival of young women with invasive breast carcinoma. *Cancer* **78**(7): 1417–1425.
- Morris EJ, Penegar S, Whitehouse LE, Quirke P, Finan P, Bishop DT, Wilkinson J, Houlston RS (2013) A retrospective observational study of the relationship between family history and survival from colorectal cancer. *Br J Cancer* **108**(7): 1502–1507.
- Ren Z-F, Liu W-S, Qin H-D, Xu Y-F, Yu D-D, Feng Q-S, Chen L-Z, Shu X-O, Zeng Y-X, Jia W-H (2010) Effect of family history of cancers and environmental factors on risk of nasopharyngeal carcinoma in Guangdong, China. *Cancer Epidemiol* **34**(4): 419–424.
- Shanmugaratnam K, Sobin LH (1991) *International Histological Classification of Tumours*. 2nd edn (WHO).
- Twu CW, Wang WY, Liang WM, Jan JS, Jiang RS, Chao J, Jin YT, Lin JC (2007) Comparison of the prognostic impact of serum anti-EBV antibody and plasma EBV DNA assays in nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* **67**(1): 130–137.
- Xu FH, Xiong D, Xu YF, Cao SM, Xue WQ, Qin HD, Liu WS, Cao JY, Zhang Y, Feng QS, Chen LZ, Li MZ, Liu ZW, Liu Q, Hong MH, Shugart YY, Zeng YX, Zeng MS, Jia WH (2012) An epidemiological and molecular study of the relationship between smoking, risk of nasopharyngeal carcinoma, and Epstein–Barr virus activation. *J Natl Cancer Inst* **104**(18): 1396–1410.
- Yu KJ, Hsu WL, Chiang CJ, Cheng YJ, Pfeiffer RM, Diehl SR, Goldstein AM, Gravitt PE, Chen CJ, Hildesheim A (2009) Cancer patterns in nasopharyngeal carcinoma multiplex families in Taiwan. *Int J Cancer* **124**(7): 1622–1625.
- Yu MC, Ho JH, Lai SH, Henderson BE (1986) Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: report of a case–control study in Hong Kong. *Cancer Res* **46**(2): 956–961.
- Zell JA, Honda J, Ziogas A, Anton-Culver H (2008) Survival after colorectal cancer diagnosis is associated with colorectal cancer family history. *Cancer Epidemiol Biomarkers Prev* **17**(11): 3134–3140.

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