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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prognostic Impact of Cigarette Smoking on the Survival of Patients with Established Nasopharyngeal Carcinoma

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Abstract

Background: Cigarette smoking is associated with the etiology of nasopharyngeal carcinoma; however, the influence of smoking on survival in patients with established nasopharyngeal carcinoma remains unknown.

Methods: We retrospectively analyzed 1,849 patients with nasopharyngeal carcinoma who were categorized as never, former, and current smokers. Cumulative effect of smoking was defined in terms of pack-years. Associations between cigarette exposure and survival were estimated by Cox proportional hazards model.

Results: The risks of death, progression, locoregional relapse, and distant metastasis were significantly higher for former and current smokers (all $P \leq 0.002$) than never smokers. Heavy smokers with high pack-years had HRs for death of 3.31 [95% confidence interval (CI), 2.58–4.26; $P < 0.001$], for progression of 2.53 (95% CI, 2.03–3.16; $P < 0.001$), and for distant metastasis of 2.65 (95% CI, 1.89–3.70; $P < 0.001$). Specifically, in the cohort of 495 patients treated with intensity-modulated radiotherapy/three-dimensional conformal radiotherapy, we obtained similarly significant results. All of the survival outcomes remained significant in multivariate analyses.

Conclusions: Pretreatment cigarette smoking is an independent, poor prognostic factor for patients with nasopharyngeal carcinoma, which is associated with increased risk of death, progression, locoregional relapse, and distant metastasis, with the risk increasing with pack-years.

Impact: It is clear that cigarette smoking not only promotes carcinogenesis in the normal nasopharyngeal epithelium, but also affects the survival of patients with nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev; 1–10. ©2013 AACR.*

Introduction

Nasopharyngeal carcinoma is a nonlymphomatous, squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx. Despite improvements in the locoregional control rate because of the development of more precise imaging and radiotherapy techniques, and eradication of potential metastases by chemotherapy (1, 2), the survival of patients with advanced nasopharyngeal carcinoma remains unsatisfactory. Therefore, it is necessary to identify prognostic factors to recognize patients at high risk of failure. Recently, associations between cigarette smoking and survival have been demonstrated in several types of cancer, including colon cancer (3), renal cell carcinoma (4), squamous cell carcinoma of the head and neck (HNSCC; refs. 5 and 6), and oropharyngeal cancer (7).

However, nasopharyngeal carcinoma has a distinct epidemiology, etiology (8), and clinical manifestation (9). The highest rates of incidence are observed in Southeast Asia, especially in Southern China where the incidence of nasopharyngeal carcinoma can be as high as 20 to 30 per 100,000 (10). In contrast, nasopharyngeal carcinoma is a relatively rare disease in Europe and the United States, with an incidence of 0.5 to 2 per 100,000 (11). The gender, age, and ethnic distribution of patients with nasopharyngeal carcinoma from different regions of China are far from uniform (8). The nasopharyngeal carcinoma–endemic populations have a particularly high intake of salt-preserved food, which is a unique risk factor for nasopharyngeal carcinoma; the potential of a high intake of salt-preserved food to lead to the development of malignant nasal and nasopharyngeal tumors is supported by data from rat models (12). More importantly, Epstein-Barr virus (EBV) plays a strongly causal role in the occurrence and development of nasopharyngeal carcinoma (13), whereas human papillomavirus is related to the etiology and prognosis of HNSCC (14). In addition, widely documented patterns of familial aggregation have demonstrated that some individuals have a genetic susceptibility to nasopharyngeal carcinoma (8). To

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date, numerous case–control studies (15–17) examining cigarette smoking and the etiology of nasopharyngeal carcinoma have established that tobacco smoking is a consensus risk factor for this type of cancer (18); however, it is worth noting that an estimated two thirds of cases of World Health Organization type I (keratinizing squamous cell carcinoma) nasopharyngeal carcinoma are attributable to smoking, whereas type II (nonkeratinizing squamous carcinoma) and type III (undifferentiated carcinomas) nasopharyngeal carcinoma are not associated with smoking (19). The key issue related to nasopharyngeal carcinoma is that around 25%, 12%, and 63% of patients in North America have type I, II, and III, respectively whereas the histological distribution in Southern Chinese patients is 2%, 3%, and 95%, respectively (9). In addition, radiotherapy with or without chemotherapy, as the standard treatment for nasopharyngeal carcinoma (9), is more likely to be affected by smoking compared with surgery, which is the major therapeutic strategy for other types of head and neck cancers.

The association between cigarette smoking history and survival in patients with nasopharyngeal carcinoma remains to be explored. Therefore, we performed this study to elucidate the effect of cigarette smoking history on the clinicopathologic features and survival of patients with nasopharyngeal carcinoma.

Materials and Methods

Patient characteristics

Between January 2005 and May 2007, all newly diagnosed with biopsy-proven nasopharyngeal carcinoma (International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3] C11, C11.0 to C11.9) patients who were hospitalized at Sun Yat-sen University Cancer Center were entered into our study. We excluded patients who were diagnosed with distant metastases before initial treatment by clinical symptoms, physical examinations, and imaging methods including chest radiography, bones scan, magnetic resonance imaging (MRI), and abdominal sonography. Medical records were reviewed to extract data on the clinicopathological features and smoking history of the patients, including age, gender, histological type, titer of immunoglobulin A against viral capsid antigen (VCA-IgA) before treatment, alcohol drinking status, smoking status at diagnosis, number of cigarettes smoked per day, number of years of smoking, and number of years since cessation. All patients were restaged according to the seventh edition of the AJCC/UICC Staging System for nasopharyngeal carcinoma (20).

Treatment and follow-up

All patients were treated by definitive radiotherapy. Details of the radiation techniques have been described previously (21, 22). In addition, institutional guidelines recommended no chemotherapy for patients with stage I or II disease, and both induction or adjuvant chemotherapy and concomitant chemotherapy for patients with stage III to IV disease, as defined by the sixth edition of the AJCC/UICC Staging System for nasopharyngeal carcinoma or the Chinese 1992 Staging System for nasopharyngeal carcinoma at that time. Induction or adjuvant chemotherapy consisted of cisplatin with 5-fluorouracil, cisplatin with taxoids, or a triplet of cisplatin and 5-fluorouracil plus taxoids every 3 weeks for 2 to 3 cycles. Concomitant chemotherapy consisted of cisplatin on weeks 1, 4, and 7 of radiotherapy, or cisplatin given weekly.

Patients were followed up every 3 months during the first 2 years, and every 6 months thereafter until death. Patients with relapse, distant metastasis, or persistent disease were administered salvage treatments including re-irradiation, 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 endpoints

We mainly explored the associations between survival and cigarette smoking in terms of: (i) smoking status at diagnosis—patients were classified as never smokers (defined as never smoking before treatment), former smokers (defined as former smokers who had stopped smoking for 1 year or more before treatment), and current smokers (defined as smoking until the day of hospitalization or smokers who had stopped smoking for less than 1 year); and (ii) the cumulative effects of smoking in terms of pack-years, which was defined as the equivalent of smoking one pack of cigarettes per day for 1 year.

Our primary endpoint was overall survival (OS), defined as the time from treatment to death from any cause. Secondary endpoints were progression-free survival (PFS), defined as the time from treatment to disease progression or death from any cause, whichever occurred first; locoregional relapse-free survival (LRFS), defined as the time from treatment to the first locoregional relapse; and distant metastasis-free survival (DMFS), defined as the time from treatment to the first distant metastasis.

Statistical methods

All endpoints were examined using Kaplan–Meier methods and the log-rank test. Univariate survival analyses were performed in terms of smoking status at diagnosis and pack-years. Multivariate analyses were performed using the Cox proportional hazards model adjusting for basic characteristics such as age, gender, etc. Comparisons of demographic, clinical, and pathologic variables were performed using the χ^2 test or Fisher exact test for nominal variables as appropriate, or the Kruskal–Wallis test for ordinal categorical variables like T-stage, N-stage, and clinical stage. For continuous variables such as pack-years and age, we explored the effect using restricted cubic splines nested within Cox models by RCS-macro of SAS (SAS Institute); if there was linear effect, cutoff scores of the continuous variable were subsequently selected based on receiver operating characteristic (ROC) curve analysis (23). The sensitivity and specificity of each endpoint was plotted, thus generating ROC curves. The score closest to the point with both

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maximum sensitivity and specificity (i.e., the point [0.0, 1.0] on the curve) was selected as the optimal cutoff score for prediction of survival. Two-sided *P* values less than 0.05 were considered significant.

Results

Treatment profiles, patterns of treatment failure, and survival

A total of 1,849 nasopharyngeal carcinoma patients were included in this study. After restaging according to the seventh edition of the AJCC/UICC Staging System, the clinical stage distribution of the 1,849 patients was: stage I, 90 (4.9%); stage II, 481 (26.0%); stage III, 796 (43.1%), and stage IV 482 (26.0%). Overall, 433/1,849 (23.4%) patients were treated with radiotherapy alone and 1,416/1,849 (76.6%) received radiotherapy plus chemotherapy. Of these 1,416 patients, 455 patients (32.1%) received induction chemotherapy and 522 patients (36.9%) received concomitant chemotherapy; a combination of induction and concomitant chemotherapy, concomitant and adjuvant chemotherapy, or the triplet of induction, concomitant, and adjuvant chemotherapy were administered to 363/1,416 (25.6%), 50/1,416 (3.5%), and 26/1,416 (1.8%) patients, respectively. With respect to radiotherapy, 1,354/1,849 (73.2%) were treated with conventional techniques, 457/1,849 (24.7%) with intensity-modulated radiotherapy (IMRT), and 38/1,849 (2.1%) with three-dimensional conformal radiotherapy (3DCRT).

Within a median follow-up duration of 73.5 months (range, 1.7–96.8 months), 150/1,849 (8.1%) patients developed locoregional relapse, 233/1,849 (12.6%) developed distant metastases, and 378/1,849 (20.4%) died. Twenty patients (1.1%) developed both locoregional relapse and distant metastases. The 3- and 5-year survival rates were as follows: OS, 88.8% and 82.2%; PFS, 79.5% and 74.2%; LRFS, 93.6% and 91.8%; and DMFS, 89.3% and 87.0%.

Demographic and clinicopathologic characteristics

The proportions of former smokers, current smokers, and never smokers were 9.1% (168/1849), 39.7% (734/1849) versus 51.2% (947/1849) in the entire population, and 9.7% (48/495), 36.4% (180/495) versus 53.9% (267/495) in the cohort of patients treated with IMRT/3DCRT. As shown in Table 1, there were no differences in the distribution of histological type or radiotherapy techniques for the entire patient cohort when stratified by smoking status. However, significant differences were observed in terms of age, gender, drinking status, VCA-IgA titer, T-stage, N-stage, clinical stage, and chemotherapy approach. Patients older than 40 years of age, and male patients with a drinking history were more frequent in the former and current smokers. There was a trend for a higher VCA-IgA titer among former and current smokers. In addition, the proportions of patients with advanced T-stage, N-stage, or clinical stage were higher for former and current smokers than never smokers. Accordingly, the proportion of patients adopting chemotherapy was higher for former and current smokers.

In the cohort of patients treated with IMRT/3DCRT, there were no significant differences in the distributions of histological type and chemotherapy when stratified by smoking status. Similarly to the entire population, the proportions of patients treated with IMRT/3DCRT who were older than 40 years of age, male with a positive drinking history, with a higher VCA-IgA titer, or with advanced T-stage, N-stage, or clinical stage were higher for former and current smokers.

Impact of cigarette smoking on survival in univariate analysis

In the entire population, OS, PFS, LRFS, and DMFS were all significantly poorer for former and current smokers than never smokers (Fig. 1). OS at 5 years was 75.4% for former smokers and 75.6% for current smokers versus 88.4% for never smokers (log-rank test, $P < 0.001$ and $P < 0.001$, respectively); the 5-year PFS rates were 67.8% and 65.0% versus 82.4% ($P < 0.001$ and $P < 0.001$, respectively); the 5-year LRFS rates were 88.6% and 89.1% versus 94.4% ($P < 0.001$, respectively); and the 5-year DMFS rates were 81.1% and 83.5% versus 90.7% ($P < 0.001$ and $P < 0.001$, respectively). Considering small number of former smokers and the similar survival rates between former and current smokers, we combined them into a single group—the smoking history group, the 5-year survival rates of which were as follow: OS 75.6%, PFS 65.6%, LRFS 89.0%, and DMFS 83.0% (Supplementary Fig. S1).

The cumulative effect of smoking was also strongly associated with the survival of patients with nasopharyngeal carcinoma. Among patients with smoking history, 32, 22, and 22 pack-years were identified as the cutoff scores for heavy and light smokers associated with OS, PFS, and DMFS, respectively. Heavy smokers had an HR of death of 3.31 [95% confidence interval (CI), 2.58–4.26; log-rank test, $P < 0.001$], HR of progression of 2.53 (95% CI, 2.03–3.16; $P < 0.001$), and HR of distant metastasis of 2.65 (95% CI, 1.89–3.70; $P < 0.001$) compared with light smokers (Fig. 2)

In the cohort of patients treated with IMRT/3DCRT, current smokers or former smokers also had higher risks of death ($P < 0.001$, $P = 0.002$) and disease progression ($P < 0.001$, $P = 0.004$) than never smokers (Supplementary Fig. S2a and S2b). The significant differences remained unchanged when combined current and former smokers into the smoking history group (Supplementary Fig. S3). And among this group, heavy smokers with more than 25 pack-years of cigarettes had an HR of death of 3.61 (95% CI, 2.12–6.14; $P < 0.001$), and those with more than 16 pack-years had an HR of progression of 3.01 (95% CI, 1.83–4.97; $P < 0.001$) compared with light smokers (Supplementary Fig. S2c and S2d).

Impact of cigarette smoking on survival in multivariate analysis

Using restricted cubic splines nested within Cox models, the variables of age and pack-years were tested in multivariate analysis in continuous and nonlinear fashion. Resultantly, both of them showed linear effects in

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Table 1. Demographic and clinicopathologic characteristics of the study population stratified by smoking status

	The entire population				The IMRT/3DCRT cohort			
	Never smoker (*N* = 947)	Former smoker (*N* = 168)	Current smoker (*N* = 734)		Never smoker (*N* = 267)	Former smoker (*N* = 48)	Current smoker (*N* = 180)	
Factor	***N* (%)**	***N* (%)**	***N* (%)**	***P***	***N* (%)**	***N* (%)**	***N* (%)**	***P***
Age group				<0.001[a]				<0.001[a]
≤30	85 (9.0)	2 (1.2)	36 (4.9)		25 (9.4)	1 (2.1)	9 (5.0)	
31–40	311 (32.8)	25 (14.9)	167 (22.8)		85 (31.8)	6 (12.5)	47 (26.1)	
41–50	289 (30.5)	57 (33.9)	243 (33.1)		88 (33.0)	22 (45.8)	56 (31.1)	
51–60	174 (18.4)	55 (32.7)	192 (26.2)		43 (16.1)	9 (18.8)	38 (21.1)	
61–70	73 (7.7)	24 (14.3)	82 (11.2)		22 (8.2)	8 (16.7)	25 (13.9)	
≥71	15 (1.6)	5 (3.0)	14 (1.9)		4 (1.5)	2 (4.2)	5 (2.8)	
Gender				<0.001				<0.001
Male	509 (53.7)	163 (97.0)	726 (98.9)		157 (58.8)	45 (93.8)	175 (97.2)	
Female	438 (46.3)	5 (3.0)	8 (1.1)		110 (41.2)	3 (6.2)	5 (2.8)	
Drinking status				<0.001[b]				<0.001[b]
Never	908 (95.9)	125 (74.4)	537 (73.2)		259 (97.0)	37 (77.1)	120 (66.7)	
Former	6 (0.6)	17 (10.1)	5 (0.7)		3 (1.1)	5 (10.4)	3 (1.7)	
Current	33 (3.5)	26 (15.5)	192 (26.2)		5 (1.9)	6 (12.5)	57 (31.6)	
VCA-IgA				0.001				0.005
≤1:160	465 (49.1)	81 (48.2)	292 (39.8)		149 (55.8)	24 (50.0)	72 (40.0)	
>1:160	482 (50.9)	87 (51.8)	442 (60.2)		118 (44.2)	24 (50.0)	108 (60.0)	
Histological type				0.348[b]				0.296[b]
I	4 (0.4)	1 (0.6)	1 (0.1)		1 (0.4)	0 (0)	0 (0)	
II	56 (5.9)	7 (4.2)	32 (4.4)		20 (7.5)	1 (2.1)	7 (3.9)	
III	887 (93.7)	160 (95.2)	701 (95.5)		246 (92.1)	47 (97.9)	173 (96.1)	
T-stage				0.042[a]				0.004[a]
T1	144 (15.2)	25 (14.9)	80 (10.9)		51 (19.1)	8 (16.7)	21 (11.7)	
T2	250 (26.4)	41 (24.4)	198 (27.0)		74 (27.7)	10 (20.8)	38 (21.1)	
T3	356 (37.6)	68 (40.5)	271 (36.9)		99 (37.1)	21 (43.8)	75 (41.7)	
T4	197 (20.8)	34 (20.2)	185 (25.2)		43 (16.1)	9 (18.8)	46 (25.6)	
N-stage				<0.001[a]				0.066[a]
N0	175 (18.5)	54 (32.1)	94 (12.8)		61 (22.8)	18 (37.5)	38 (21.1)	
N1	555 (58.6)	82 (48.8)	390 (53.1)		150 (56.2)	22 (45.8)	96 (53.3)	
N2	190 (20.1)	25 (14.9)	203 (27.7)		45 (16.9)	7 (14.6)	37 (20.6)	
N3	27 (2.9)	7 (4.2)	47 (6.4)		11 (4.1)	1 (2.1)	9 (5.0)	
Clinical stage				<0.001[a]				0.015[a]
I	51 (5.4)	14 (8.3)	25 (3.4)		23 (8.6)	6 (12.5)	11 (6.1)	
II	269 (28.4)	42 (25.0)	170 (23.2)		81 (30.3)	9 (18.8)	38 (21.1)	
III	408 (43.1)	72 (42.9)	316 (43.1)		111 (41.6)	23 (47.9)	78 (43.3)	
IVa	192 (20.3)	33 (19.6)	177 (24.1)		41 (15.4)	9 (18.8)	44 (24.4)	
IVb	27 (2.9)	7 (4.2)	46 (6.3)		11 (4.1)	1 (2.1)	9 (5.0)	
Chemotherapy				<0.001				0.098
No	225 (23.8)	59 (35.1)	149 (20.3)		69 (25.8)	18 (37.5)	40 (22.2)	
Yes	722 (76.2)	109 (64.9)	585 (79.7)		198 (74.2)	30 (62.5)	140 (87.8)	
Radiotherapy				0.504[b]				
IMRT	246 (26.0)	45 (26.8)	166 (22.6)					
3DCRT	21 (2.2)	3 (1.8)	14 (1.9)					
CRT	680 (71.8)	120 (71.4)	554 (75.5)					

NOTE: A former smoker was defined as an individual who had not smoked for 12 months or more at enrollment.

[a]Kruskal–Wallis test.

[b]Fisher's exact probabilities test.

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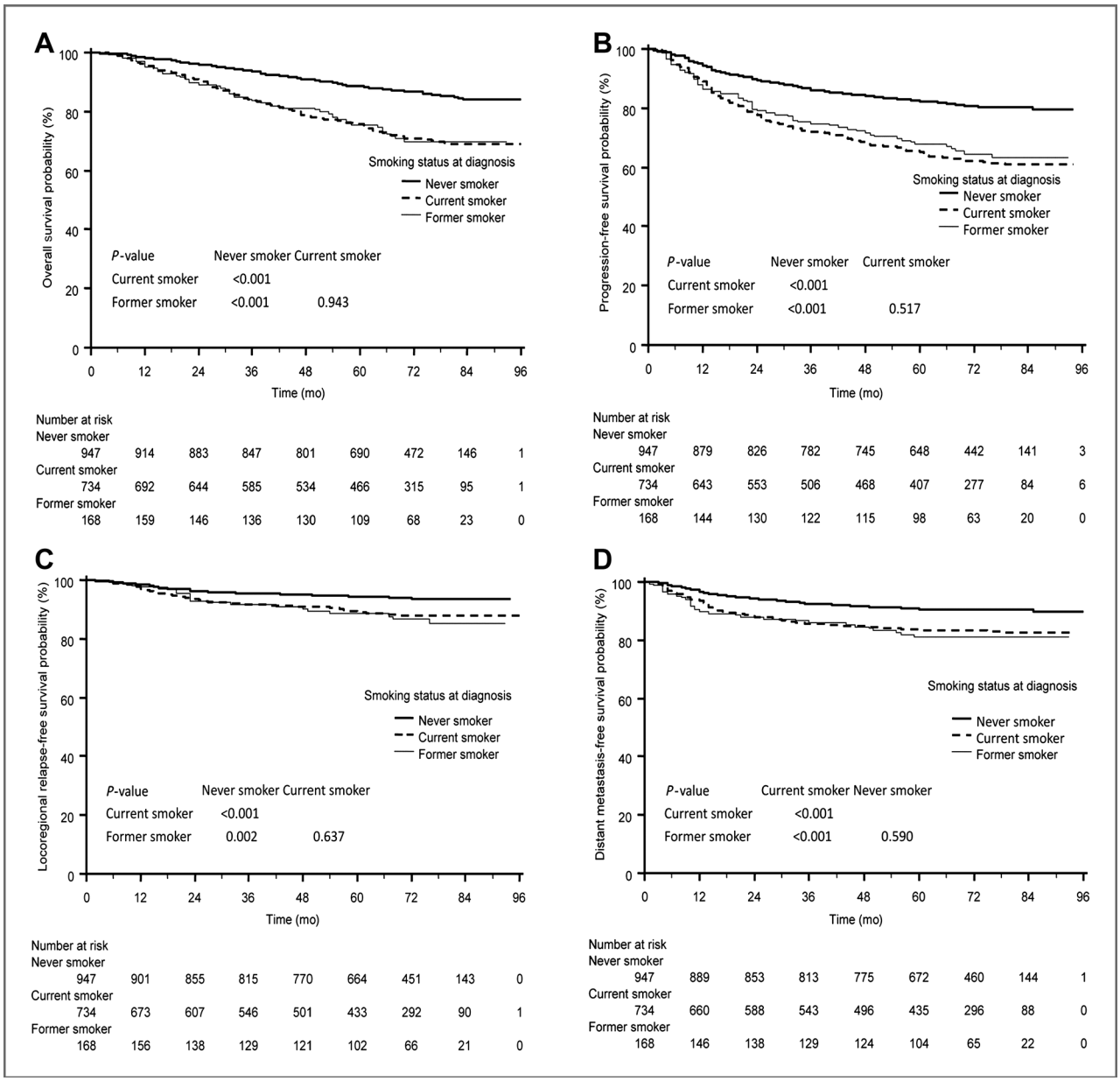

Figure 1. (A) Overall survival, (B) progression-free survival, (C) locoregional relapse-free survival, and (D) distant metastasis-free survival curves of patients in the entire population according to smoking status at diagnosis. A former smoker was defined as an individual who had not smoked for 12 months or more at enrollment.

most cases. However, the age was excluded as a covariate when we analyzed the impact of smoking history in PFS in the entire population; the pack-years was showed to be a nonsignificant prognosis of LRFS for patients with smoking history in the entire population (see Supplementary Material).

In multivariate analysis, smoking history (former and current smokers) versus no smoking history (never smokers) and high pack-years versus low pack-years, together with age (continuous), T-stage, and N-stage were found to be significant, independent predictors of overall survival for both the entire population and patients treated with IMRT/3DCRT (Table 2). In addition, we also assessed the association between smoking history and OS across strata of other potential predictors of patient outcome in the entire population (Table 3). The effect of smoking history on the risk of death was not significantly modified by age, titer of VCA-IgA, clinical stage of disease, chemotherapy approach, or radiation technique. However, the impact of smoking history in increasing risk of death was not observed among female patients (adjusted HR = 1.75; 95% CI, 0.66–4.64; $P = 0.257$) and patients with drinking history (adjusted HR = 1.78; 95% CI, 0.76–4.16; $P = 0.187$).

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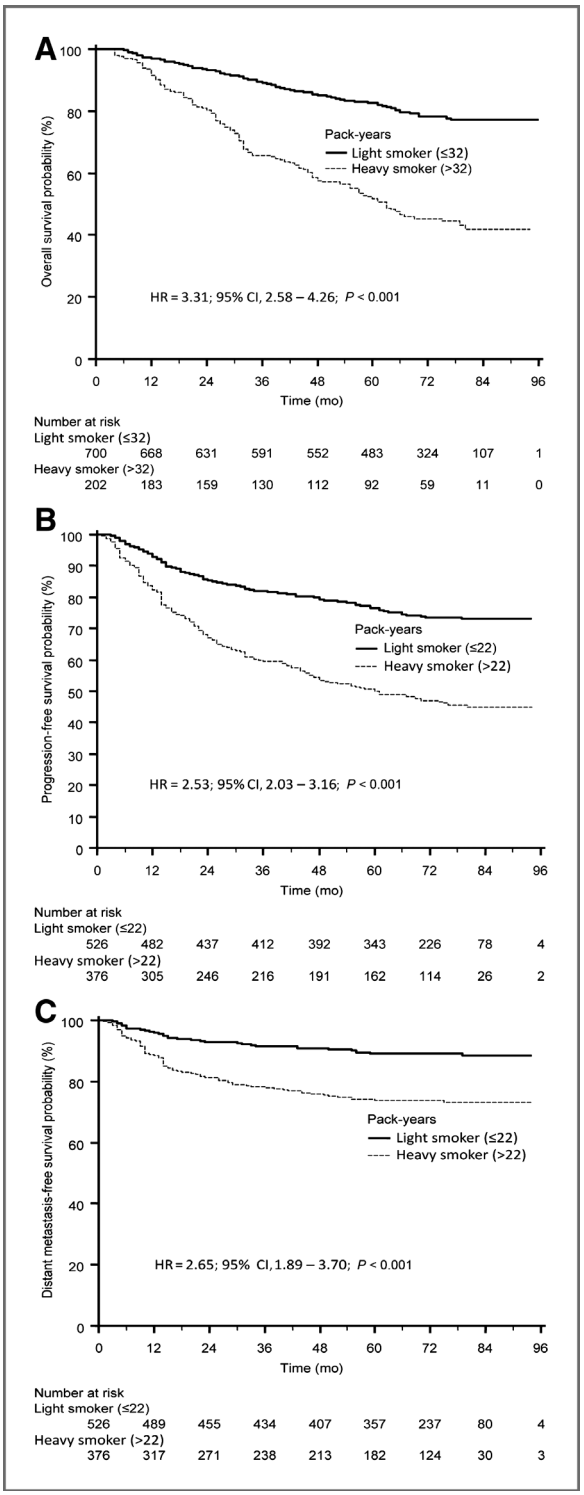

Figure 2. (A) Overall survival, (B) progression-free survival, and (C) distant metastasis-free survival curves of patients according to pack-years. A pack-year was defined as the equivalent of smoking one pack of cigarettes per day for 1 year.

In second analysis (Table 4), former smokers had an HR of death of 1.46 (95% CI, 1.20–1.78; $P < 0.001$) and HR of progression of 1.41 (95% CI, 1.19–1.68; $P < 0.001$) compared with never smokers; whereas current smokers had an HR of death of 1.67 (95% CI, 1.26–2.21; $P < 0.001$) and HR of progression of 1.74 (95% CI, 1.37–2.21; $P < 0.001$) compared with never smokers. The risks of death and progression for heavy smokers were higher than light smokers, with HRs of 2.10 (95% CI, 1.58–2.79; $P < 0.001$) and 1.64 (95% CI, 1.23–2.19; $P < 0.001$), respectively. When the pack-years was evaluated as a continuous variable, the HRs for death and progression increased by 2% per pack-year.

In the cohort of patients treated with IMRT/3DCRT, former smokers had an HR of death of 1.51 (95% CI, 1.05–2.18; $P = 0.026$) and HR of progression of 1.44 (95% CI, 1.03–2.01; $P = 0.033$) compared with never smokers, whereas current smokers had an HR of death of 1.90 (95% CI, 1.12–3.22; $P = 0.017$) and HR of progression of 2.37 (95% CI, 1.50–3.75; $P < 0.001$) compared with never smokers. In addition, compared with light smokers, the HRs for death and progression for heavy smokers were extremely high, at 2.41 (95% CI, 1.17–4.96; $P = 0.017$) and 2.60 (95% CI, 1.44–4.69; $P = 0.002$), respectively. Similarly, when the pack-years was evaluated as a continuous variable, the HRs for death and progression increased by 3% per pack-year (Table 4).

Discussion

Numerous case–control studies have convincingly demonstrated that cigarette smoking greatly increases the risk of developing nasopharyngeal carcinoma (15–17); however, the possibility of cigarette smoking being a predictor of overall survival in nasopharyngeal carcinoma has only been shown in one study (24), the analyzed data extracted from an epidemiological investigation which was limited with respect to the treatment regimens, follow-up care, disease stage, treatment outcomes and other prognostic factors. This study is the first investigation of a large number of patients ($N = 1,849$) to demonstrate that cigarette smoking is an independent, poor prognostic factor for survival in patients with established nasopharyngeal carcinoma after adjusting for age (continuous), gender, drinking status, histological type, T-stage, N-stage, VCA-IgA titer ($\leq$ and >1:160), radiotherapy techniques, and chemotherapy regimens. We subsequently evaluated the increased risk of death and progression in terms of pack-years of cigarettes. In addition, we performed a specific analysis of the cohort of 495 patients treated with IMRT/3DCRT to account for the heterogeneity of radiotherapy techniques. According to these analyses, it is clear that cigarette smoking not only promotes carcinogenesis in the normal nasopharyngeal epithelium (15–17), but also affects the survival of patients with nasopharyngeal carcinoma. This result is not unexpected. In a recent study of patients with oral, pharyngeal, and larynx cancer that did not include patients with nasopharyngeal carcinoma, smoking was associated with an increased cancer-specific mortality (25). Previous studies have shown that smoking status at diagnosis is associated with the survival of patients with HNSCC (5, 6), and

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Table 2. Multivariable Cox proportional hazards models for overall survival in terms of smoking history (smoking history vs. no smoking history) and pack-years (heavy vs. light smokers)

	The entire population				The IMRT/3DCRT cohort			
	Smoking history ($N = 1,849$)		Pack-years ($N = 902$)[a]		Smoking history ($N = 495$)		Pack-years ($N = 228$)[b]	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (continuous)	1.04 (1.03–1.05)	<0.001	1.03 (1.02–1.04)	<0.001	1.05 (1.03–1.07)	<0.001	1.03 (0.99–1.06)	0.115
Gender	0.96 (0.70–1.33)	0.811	0.98 (0.45–2.16)	0.961	1.15 (0.57–1.65)	0.693	1.96 (0.69–5.57)	0.210
Drinking	1.02 (0.82–1.28)	0.847	0.95 (0.74–1.21)	0.681	0.97 (0.57–1.65)	0.923	0.85 (0.47–1.54)	0.598
VCA-IgA[c]	1.02 (0.83–1.26)	0.830	1.02 (0.78–1.32)	0.899	1.13 (0.71–1.81)	0.612	1.00 (0.57–1.77)	0.990
Histological type	1.08 (0.70–1.65)	0.738	1.01 (0.60–1.72)	0.965	1.30 (0.41–4.17)	0.658	2.12 (0.28–15.91)	0.467
T-stage	1.62 (1.43–1.82)	< 0.001	1.45 (1.25–1.68)	< 0.001	1.62 (1.39–2.49)	< 0.001	1.52 (1.08–2.14)	0.016
N-stage	1.70 (1.49–1.95)	< 0.001	1.64 (1.40–1.93)	< 0.001	1.53 (1.12–2.08)	0.007	1.64 (1.12–2.40)	0.011
Radiotherapy	0.94 (0.82–1.07)	0.331	0.99 (0.85–1.16)	0.924	1.15 (0.41–3.21)	0.794	1.15 (0.34–3.94)	0.821
Chemotherapy	0.96 (0.90–1.02)	0.194	0.98 (0.91–1.07)	0.683	0.91 (0.78–1.07)	0.267	0.88 (0.73–1.06)	0.179
Smoking history	1.73 (1.32–2.27)	< 0.001	–	–	2.08 (1.14–3.79)	0.017	–	–
Pack-years	–	–	2.10 (1.58–2.79)	< 0.001	–	–	2.41 (1.17–4.96)	0.017

[a]Pack-years: $\leq$ vs. > 32.
[b]Pack-years: $\leq$ vs. > 25.
[c]Titer of VCA-IgA: $\leq$ vs. > 1:160.

the risk of death increased with increasing exposure to tobacco as measured in pack-years or years of smoking (26). Smoking was also identified as an indicator of poor prognosis in patients with oropharyngeal cancer, regardless of the tumor p16 status or treatment (7). In addition, patients with renal cell carcinoma and a history of smoking were more likely to have advanced pathologic features and poorer survival outcomes (4). Similar significant associations between smoking and poorer disease-free survival and time to recurrence have also been observed in patients with colon cancer (3).

Recently, Duffy and colleagues found that smoking was independently associated with a higher serum interleukin-6 (IL-6) level among patients with head and neck cancer (27), and a higher IL-6 level was predictive of an increased risk of recurrence and poorer OS (28). In nasopharyngeal carcinoma, IL-6 facilitates tumor carcinogenesis and malignancy enhancement via activation of the *STAT3*, and a higher IL-6 level is associated with advanced stage nasopharyngeal carcinoma (29). Second, it has been demonstrated that smoking is involved in EBV activation and smokers have increased seropositivity for the EBV VCA-IgA antibody (16); and EBV status is strongly associated with the risk of developing nasopharyngeal carcinoma (30) and patients' LRFS and OS (31, 32). Therefore, via EBV activation, smoking may also contribute to the survival differences between patients who smoke and those who do not. Moreover, evidence indicates that smoking exacerbates tissue hypoxia and can lead to smoking-induced tissue hypoxia in healthy human smokers (33), and inhalation of carbon monoxide—one component of cigarette smoke—can reduce the control of tumors by radiotherapy in animal models (34). In addition, patients with head and neck cancer (including nasopharyngeal carcinoma) with a higher smoking status have higher venous blood levels of carboxyhemoglobin, which results in reduced oxygen supply to the tumors (35). It is known that hypoxia induces the expression of a variety of genes associated with an aggressive malignant phenotype, including genes involved in stem cell maintenance, invasion, angiogenesis, and extravasation (36). The transcription of hypoxia-related genes, which is predominantly mediated by the hypoxia-inducible factor-1α (*HIF-1α*) in cooperation with *HIF-2α*, promotes tumor angiogenesis and the proliferation, invasion, and metastasis of tumor cells (37). Furthermore, tumor hypoxia has been acknowledged to affect the responses to both radiotherapy (38) and chemotherapy (39), and has been associated with poorer OS in HNSCC (40). In addition, basic research has demonstrated that cigarette smoke condensate promotes chemoresistance via *Akt*-mediated regulation of the activity of the ATP-binding cassette transporter G2, and may also contribute to tumor recurrence, invasion, or metastasis by increasing the proportion of cancer stem-like cells (41). Thus, the presence of residual smoke condensate in former and current smokers may reduce the effect of chemotherapy and promote tumor progression.

In this study, the impact of smoking in increasing risk of death was not observed among female patients and patients with drinking history. This may have been because of small number of patients in the individual subgroups. Moreover, it was interesting that there were no significant differences in the survival outcomes of former and current smokers; both groups had similarly

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Table 3. Subgroup analysis of OS in terms of smoking history vs. no smoking history by the characteristics of patients in the entire population

Factor	5-year OS rate (%)	*P* for OS by each factor	No. of events/no. at risk		Adjusted HR (95% CI)[a]	*P* for smoking history vs. no smoking history
			No smoking history	Smoking history		
Overall	82.2		126/947	252/902	1.73 (1.32–2.27)	<0.001
Age (year)		<0.001				
≤52	86.4		83/723	126/589	1.79 (1.26–2.54)	0.001
>52	71.8		43/224	126/313	2.02 (1.31–3.14)	0.002
Gender		<0.001				
Male	80.4		65/509	245/889	1.69 (1.27–2.24)	<0.001
Female	87.6		61/438	7/13	1.75 (0.66–4.64)	0.257
Drinking status		0.017				
Yes	77.8		7/39	65/240	1.78 (0.76–4.16)	0.187
No	83.0		119/908	187/662	1.79 (1.34–2.38)	<0.001
VCA-IgA		0.004				
≤1:160	84.7		53/465	94/373	1.77 (1.25–2.52)	0.001
>1:160	80.1		73/482	158/529	1.78 (1.34–2.36)	<0.001
Clinical stage		<0.001				
I + II	92.6		11/320	37/251	3.67 (1.54–8.77)	0.003
III + IV	77.4		115/627	215/651	1.76 (1.32–2.35)	<0.001
Chemotherapy		0.001				
Yes	80.5		104/722	210/694	1.74 (1.28–2.35)	<0.001
No	87.5		22/225	42/208	2.10 (1.05–4.18)	0.035
Radiation technique		0.007				
IMRT/3DCRT	86.9		23/267	55/228	2.08 (1.14–3.79)	0.017
Conventional	80.4		103/680	197/674	1.60 (1.18–2.17)	0.003

[a]Adjusted for age (continuous), gender, drinking status, histological type, T-stage, N-stage, VCA-IgA titer (≤ and > 1:160), radiation techniques, and chemotherapy regimens.

poor survival outcomes compared with never smokers, even after adjusting for factors such as drinking behavior. Heavy smokers—in terms of high pack-years—are likely to have been subjected to the prolonged, severe, cumulative effects of smoking, and their relatively poor survival rates also demonstrated that the influence of smoking develops after long-term exposure. Therefore, despite the fact that former smokers were patients who had stopped smoking for at least 1 year, they may not have totally eliminated the residual condensates of cigarette smoke during this time, and the ability of smoking to enhance the IL-6 level, activate EBV, exacerbate tissue hypoxia, and promote chemoresistance and tumor progression may have already occurred and are likely to be maintained after stopping smoking. Finally, a recent study (42) found that 13% of cancer patients who did not smoke in the 7 days before surgery had resumed smoking within 12 months after surgery; their resumption of smoking was related to a higher perceived difficulty of quitting and lower perceptions of their cancer-related risk. Research has shown that continued smoking after diagnosis has immediate adverse impacts, including reduced efficacy of cancer treatment (5, 41), increased proportions of cancer stem-like cells (41), higher rates of treatment complications and side effects (43, 44), higher treatment-related weight loss (45), and a poorer quality of life (46). Unfortunately, we did not collect data on the patients who resumed or continued smoking during treatment or follow-up in this study; therefore, the possibility that some former smokers resumed smoking during treatment or follow-up cannot be ignored.

The following limitations of this study deserve comment. First, like other retrospective studies in nasopharyngeal carcinoma, the treatment regimens were not totally consistent with the latest NCCN guidelines, for example, the number of patients with stage I and II disease (Table 1) was not equal to the number of patients who received radiotherapy alone. This is mainly because the patients were initially staged according to the sixth edition of the AJCC/UICC Staging System or the Chinese 1992 Staging System for nasopharyngeal carcinoma before making treatment decisions, whereas we restaged the patients according to the seventh edition of the AJCC/UICC Staging System during the retrospective analysis. In addition, during the period when the patients were treated, many patients were encouraged to participate in

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Table 4. Effect of various smoking exposure measures on overall survival and progression-free survival in patients with nasopharyngeal carcinoma after adjusting for significant prognostic factors[a]

	The entire population		The IMRT/3DCRT cohort	
	Overall survival	Progression-free survival	Overall survival	Progression-free survival
Variables	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Smoking status at diagnosis				
Former vs. never	1.46 (1.20–1.78)	1.41 (1.19–1.68)	1.51 (1.05–2.18)	1.44 (1.03–2.01)
Current vs. never	1.67 (1.26–2.21)	1.74 (1.37–2.21)	1.90 (1.12–3.22)	2.37 (1.50–3.75)
Pack-years				
Heavy vs. light	2.10[b] (1.58–2.79)	1.64[c] (1.23–2.19)	2.41[d] (1.17–4.96)	2.60[e] (1.44–4.69)
Pack-years (continuous)	1.02 (1.01–1.02)	1.02 (1.01–1.02)	1.03 (1.01–1.04)	1.03 (1.02–1.04)

[a]Adjusted for age (continuous), gender, drinking status, histological type, T-stage, N-stage, VCA-IgA titer ($\leq$ and >1:160), radiation techniques, and chemotherapy regimens.
[b]Pack-years: $\leq$ versus >32.
[c]Pack-years: $\leq$ versus >22.
[d]Pack-years: $\leq$ versus >25.
[e]Pack-years: $\leq$ versus >16.

randomized trials, which also resulted in heterogeneous treatment strategies. However, we conducted multivariate analyses accounting for radiation techniques and chemotherapy approaches, and specifically analyzed the IMRT/3DCRT cohort independently. Second, we were unable to collect adequate information about the patients' pretreatment EBV DNA copy number, which has been shown to be superior to the serum EBV VCA-IgA antibody titer for making prognostic predictions in nasopharyngeal carcinoma (47). However, the VCA-IgA antibody titer, and not the EBV DNA copy number, has been demonstrated to be highly associated with smoking status in nasopharyngeal carcinoma (16). Future studies based on the EBV DNA copy number are being planned. Finally, smoking and drinking status at diagnosis were extracted from medical records, rather than determined by standardized questionnaires at enrollment. This is an inevitable limitation caused by retrospective study. However, this sort of data are of high reliability because of medical records' strong validity of law in China.

In conclusion, this study of 1,849 patients demonstrated that pretreatment smoking history was an independent, poor prognostic factor for nasopharyngeal carcinoma patients; smoking was associated with an increased risk of death, progression, locoregional relapse and distant metastasis, with the risks increasing with the number of pack-years, years of smoking, and cigarettes per day.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.-Y. OuYang, W. Deng, F.-Y. Xie
Development of methodology: P.-Y. OuYang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.-Y. OuYang, Z. Su, Y.-P. Mao
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.-Y. OuYang, Z. Su, Y.-P. Mao, Q. Liu, W. Deng, F.-Y. Xie
Writing, review, and/or revision of the manuscript: P.-Y. OuYang, Z. Su, Y.-P. Mao, W. Deng, F.-Y. Xie
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.-Y. OuYang, Z. Su, Y.-P. Mao, W. Deng, F.-Y. Xie
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Prognostic Impact of Cigarette Smoking on the Survival of Patients with Established Nasopharyngeal Carcinoma

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