

# Combined heavy smoking and drinking predicts overall but not disease-free survival after curative resection of locoregional esophageal squamous cell carcinoma

Peng Sun<sup>1,2,\*</sup>Cui Chen<sup>3,\*</sup>Fei Zhang<sup>1,2,\*</sup>Hang Yang<sup>1,2</sup>Xi-Wen Bi<sup>1,2</sup>Xin An<sup>1,2</sup>Feng-Hua Wang<sup>1,2</sup>Wen-Qi Jiang<sup>1,2</sup>

<sup>1</sup>State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine,

<sup>2</sup>Department of Medical Oncology, Sun Yat-Sen University Cancer Center,

<sup>3</sup>Department of Oncology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, Guangdong Province, People's Republic of China

\*These authors contributed equally to this work

**Introduction:** The prognostic impact of smoking and drinking on esophageal squamous cell carcinoma (ESCC) was scarcely discussed. We investigated the prognostic value of smoking and drinking and their relationships with clinicopathological characteristics in a large cohort of patients with locoregional ESCC.

**Patients and methods:** We retrospectively analyzed 488 patients who underwent curative treatment at a single institution between January 2007 and December 2008. A chi-square test was used to evaluate the relationships between smoking and drinking and clinicopathological variables, the Kaplan–Meier method was used for 5-year overall survival (OS) and disease-free survival, and Cox proportional hazards models were applied for univariate and multivariate analyses of variables with respect to OS and disease-free survival.

**Results:** Heavy smokers were more likely to have advanced Tumor-Node-Metastases (TNM) stage and higher neutrophil/lymphocyte ratio at diagnosis ( $P < 0.05$ ). Drinkers were more likely to have advanced TNM stage, to present with a larger tumor, and to undergo multidisciplinary treatment ( $P < 0.05$ ). For patients who used neither heavy tobacco nor alcohol, used either tobacco or alcohol, and used both, the 5-year OS rates and OS times were 57.4%, 46.4%, and 39.1% ( $P < 0.05$ ) and not reached, 55.2 months, and 41.2 months ( $P < 0.05$ ), respectively. On multivariate analysis, patients who both heavily smoked and drank had 1.392 times the risk of dying during follow-up compared with neither-users (95% CI = 1.020–1.901,  $P = 0.037$ ).

**Conclusion:** We identified that combined heavy smoking and drinking might predict poor prognosis in ESCC patients.

**Keywords:** esophageal squamous cell carcinoma, smoking, drinking, survival, prognosis

## Background

Esophageal cancer is the fourth leading cause of cancer death in the People's Republic of China. In contrast to Western countries, esophageal squamous cell carcinoma (ESCC) continues to be the predominant subtype in Chinese population, with a high burden of morbidity and mortality.<sup>1–3</sup> Despite the increasing availability of treatments and anticancer drugs, the prognosis of ESCC remains unfavorable, with a 5-year overall survival (OS) rate of  $< 40\%$ .<sup>3</sup> The Tumor-Node-Metastases (TNM) staging system is widely used to stratify survival in ESCC.<sup>4</sup> In addition to the TNM system, various factors have been studied in attempts to predict prognosis in clinical practice more accurately. Recently, a series of inflammatory biomarkers have been identified as prognostic factors in patients with ESCC and other cancers, such as Glasgow

Correspondence: Feng-Hua Wang;  
Wen-Qi Jiang  
Department of Medical Oncology,  
Sun Yat-Sen University Cancer Center,  
651 Dong Feng RD East, Guangzhou,  
Guangdong Province 510060, People's  
Republic of China  
Tel/fax +86 20 8734 3351;  
+86 20 8734 3765  
Email wangfh@sysucc.org.cn;  
jiangwq@sysucc.org.cn

Prognostic Score (GPS) and neutrophil/lymphocyte ratio (NLR).<sup>5-10</sup> These inflammatory prognostic biomarkers have been increasingly appreciated, as they could be easily calculated and feasibly operated in clinical practice.

Cumulative evidence has identified tobacco smoking and alcohol drinking as significant risk factors for ESCC.<sup>1,11-16</sup> However, the prognostic value of smoking and drinking in ESCC has been less discussed. Few studies have been reported for esophageal cancer, though the data varied widely. In 2008, a study from Sweden showed that smoking was an unfavorable prognostic factor for ESCC.<sup>17</sup> Similar findings were reported by Japanese authors in 2009.<sup>18</sup> However, an Australian study then demonstrated that heavy consumption of alcohol but not smoking was associated with worse prognosis in ESCC.<sup>19</sup> In 2013, two Chinese studies declared conflicting findings regarding this issue. Zhang et al<sup>2</sup> reported that neither smoking nor drinking predicted 2-year OS or disease-free survival (DFS) in ESCC patients from Shandong province. Another study demonstrated that drinking, smoking, and areca chewing were all significant prognostic factors in ESCC patients from Taiwan province.<sup>20</sup>

Therefore, we conducted this clinical study to explore the prognostic value of smoking and drinking in a consecutive cohort of Chinese patients with locoregional ESCC who underwent surgery-based curative therapy. The objectives of the study were to evaluate the prognostic value of tobacco smoking and alcohol drinking and to investigate their relationships with other clinicopathological characteristics.

## Patients and methods

### Ethics statement

All patients provided authorized and written informed consent for their information to be stored in the Sun Yat-Sen University Cancer Center database and to be used for research. Study approval was obtained from an independent ethics committee at the Cancer Center of Sun Yat-Sen University. The study was undertaken in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki. All the methods were carried out in accordance with the approved guidelines.

### Patients

A consecutive cohort of patients who attended Sun Yat-Sen University Cancer Center between January 2007 and December 2008 was analyzed retrospectively. Four hundred eighty-eight cases who met the following criteria were included in the study: 1) the disease was pathologically diagnosed as ESCC and evaluated clinically to be at a localized or locoregional

stage (stages I–III according to the sixth edition of the American Joint Committee on Cancer [AJCC]/Union for International Cancer Control [UICC] TNM system); 2) complete clinical data and disease records were available; and 3) the disease was managed with radical esophagectomy.

Basic demographics (sex, age), details of medical history and medications, and baseline tumor characteristics (grade and stage) were collected for all patients (Table 1). Heavy smoking was defined as  $\geq 20$  lifetime pack-years.<sup>18</sup> Alcohol drinkers were defined as patients who consumed any alcoholic beverage once or more per week.<sup>14,20</sup> On cessation of treatment, each patient was followed up every 3 months at the clinic or by telephone contact and interviewed for at least 5 years. The last follow-up date was July 31, 2014.

### Statistical analysis

Relationships between smoking and drinking status and clinicopathological variables were assessed by chi-square test. Survival time was calculated from the date of diagnosis to the date of death or the last follow-up. For patients who remained alive, data were censored at the date of last contact. For the analysis of DFS, events were defined as the first locoregional recurrence or distant tumor relapse or death from any cause. Kaplan–Meier method was used to estimate the 5-year OS and 5-year DFS; log-rank test was used to determine survival differences between subgroups differing in exposure to heavy smoking and/or drinking. Cox proportional hazards models were used for univariate and multivariate analyses to determine hazard ratios (HRs) for variables with respect to OS and DFS. HRs with 95% confidence intervals (CIs) and two-sided *P*-values were reported. Alpha values of  $P < 0.05$  were considered statistically significant. All statistical analyses were performed using SPSS Version 19.0 (IBM Corporation, Armonk, NY).

## Results

### Patient characteristics and treatments

The characteristics of the study population are presented in Table 1. Data for 488 ESCC patients were analyzed (369 men and 119 women). The median age at presentation with cancer was 59 years (mean 58.4 years). Tumors were pathologically confirmed as being of highly or moderately differentiated grade in 378 patients (77.4%). Three hundred seven tumors (62.9%) were limited to the middle third of the esophagus. A total of 43 (8.8%), 228 (46.7%), and 217 (44.5%) patients were categorized as having AJCC/UICC stage I, stage II, and stage III disease, respectively. GPS and NLR were calculated to evaluate the systemic inflammatory status of each

**Table I** Baseline patient demographics and tumor characteristics

Characteristics	Total	Heavy smoking		$\chi^2$ P-value	Drinking		$\chi^2$ P-value
		Yes (n=250, 51.2%)	No (n=238, 48.8%)		Yes (n=165, 33.8%)	No (n=323, 66.2%)	
Sex				<0.001*			<0.001*
Male	369	247 (66.9%)	122 (33.1%)		163 (44.2%)	206 (55.8%)	
Female	119	3 (2.5%)	116 (97.5%)		2 (1.7%)	117 (98.3%)	
Age (years)				0.968			0.218
Mean $\pm$ SD	58.4 $\pm$ 9.2	58.3 $\pm$ 8.6	58.6 $\pm$ 9.8		57.4 $\pm$ 8.1	58.9 $\pm$ 9.6	
Median	59.00	59	59		58	59	
<60	262	134 (55.1%)	128 (48.9%)		95 (36.3%)	167 (63.7%)	
$\geq$ 60	226	116 (51.3%)	110 (48.7%)		70 (31.0%)	156 (69.0%)	
Tumor grade				0.939			0.465
I-II	378	194 (51.3%)	184 (48.7%)		131 (34.7%)	247 (65.3%)	
III	110	56 (50.9%)	54 (49.1%)		34 (30.9%)	76 (69.1%)	
Tumor location				0.209			0.439
Upper	42	20 (47.6%)	22 (52.4%)		13 (31.0%)	29 (69.0%)	
Middle	307	150 (48.9%)	157 (51.1%)		99 (32.2%)	208 (67.8%)	
Lower	139	80 (57.6%)	59 (42.4%)		53 (38.1%)	86 (61.9%)	
Tumor length				0.639			0.023*
$\leq$ 3 cm	251	126 (50.2%)	125 (49.8%)		73 (29.1%)	178 (70.9%)	
>3 cm	237	124 (52.3%)	113 (47.7%)		92 (38.8%)	145 (61.2%)	
TNM stage				0.007*			0.010*
I	43	17 (39.5%)	26 (60.5%)		11 (25.6%)	32 (74.4%)	
II	228	105 (46.1%)	123 (53.9%)		65 (28.5%)	163 (71.5%)	
III	217	128 (59.0%)	89 (41.0%)		89 (41.0%)	128 (59.0%)	
Treatment				0.108			0.009*
Surgery alone	385	190 (49.4%)	195 (50.6%)		119 (30.9%)	266 (69.1%)	
Surgery + RT/CT	103	60 (58.3%)	43 (41.7%)		46 (44.7%)	57 (55.3%)	
GPS				0.092			0.334
0	379	186 (49.1%)	193 (50.9%)		125 (33.0%)	254 (67.0%)	
I	95	58 (61.1%)	37 (38.9%)		37 (38.9%)	58 (61.1%)	
2	14	6 (42.9%)	8 (57.1%)		3 (21.4%)	11 (78.6%)	
NLR				0.014*			0.291
<2	247	113 (45.7%)	134 (54.3%)		78 (31.6%)	169 (68.4%)	
$\geq$ 2	241	137 (56.8%)	104 (43.2%)		87 (36.1%)	154 (63.9%)	

Note: \* $P < 0.05$ .

Abbreviations: SD, standard deviation; RT, radiotherapy; CT, chemotherapy; GPS, Glasgow Prognostic Score; NLR, neutrophil/lymphocyte ratio; TNM, Tumor-Node-Metastases.

patient.<sup>5-7</sup> Baseline GPSs were 0, 1, and 2 in 379 (77.7%), 95 (19.5%), and 14 (28.6%) patients, respectively. At initial diagnosis, 247 patients had NLR <2 and 241 had NLR  $\geq$ 2. Of the 488 patients included in the study, 250 (51.2%) were heavy smokers and 165 were alcohol drinkers (33.8%).

A total of 247 heavy smokers and 163 drinkers were male patients, representing a significant male predominance. Compared with never-smokers and light smokers, heavy smokers were more likely to have advanced TNM stage ( $P=0.007$ ) and higher NLR at initial diagnosis ( $P=0.014$ ). Compared with nondrinkers, alcohol drinkers were more likely to have advanced TNM stage ( $P=0.010$ ), to present with a larger tumor ( $P=0.023$ ), and to undergo multidisciplinary treatment ( $P=0.009$ ).

All patients (n=488) underwent radical esophagectomy. A total of 385 (78.9%) patients underwent radical

esophagectomy alone and 103 (21.1%) underwent radical esophagectomy combined with multimodal treatment. Adjuvant treatments were chemotherapy in 69 patients, chemoradiotherapy in 12 patients, and radiotherapy in three patients. Thirteen patients received neoadjuvant concurrent chemoradiotherapy, five underwent neoadjuvant chemotherapy, and one received neoadjuvant radiotherapy. The most common chemotherapeutic agents administered in various combinations were docetaxel (n=52), nedaplatin (n=48), cisplatin (n=30), fluorouracil (n=27), and paclitaxel (n=16). Docetaxel plus nedaplatin (n=34) was the most commonly used regimen.

## Survival analysis

Median follow-up time was 44 months (range 1–90 months). During the follow-up period, 228 patients died from ESCC

and 13 patients died from cardiovascular diseases, pulmonary diseases, and treatment-related toxicity. Median DFS and survival time for the entire patient group were 43.2 months and 59.3 months, respectively. Three-year and 5-year DFS rates were 52.7% and 42.4%, respectively; 3-year and 5-year survival rates were 59.7% and 49.6%, respectively.

In a Cox univariate model for DFS, tumor grade, tumor length, TNM stage, treatment approach, smoking status, and drinking status were all significant prognostic factors. Because both heavy smoking and drinking are risk factors for ESCC, we further explored the impact of combined heavy smoking and drinking on DFS and OS. Combined exposure (both heavy smoking and drinking) was significantly associated with impaired DFS on univariate analysis ( $P=0.022$ , HR =1.400, 95% CI =1.051–1.865). Median DFS was 58.5 months for patients who neither smoked heavily nor drank (neither-users) and 30.9 months for those exposed to both, with 5-year DFS rates of 48.5% and 35.1%, respectively (Figure 1). On multivariate analysis of DFS, both tumor grade and TNM stage were shown to be independent prognostic factors. However, combined exposure failed to independently predict unfavorable DFS on multivariate analysis (Table 2).

Univariate analysis of OS indicated that tumor length, TNM stage, treatment, GPS, smoking status, drinking status, and combined exposure status significantly predicted the clinical outcome of ESCC. Compared with neither-users, the crude HRs for those using one or both substances were 1.367 and 1.578, respectively (both  $P<0.05$ ). Multivariate analysis of OS was then performed using a Cox proportional hazards model. After adjusting for tumor length, clinical

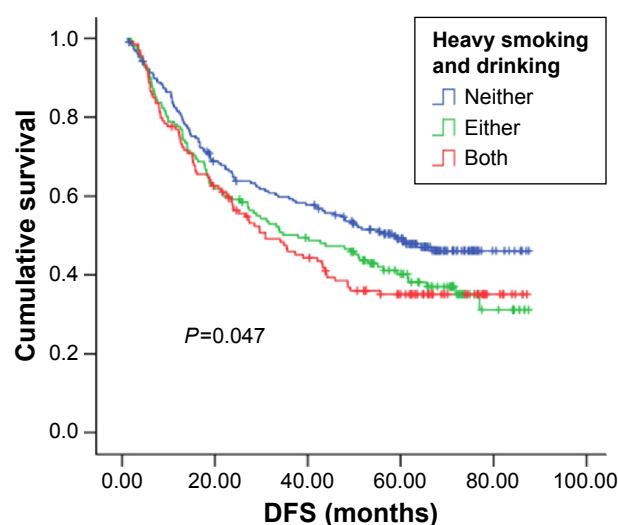
stage, treatment, and GPS, we found that patients who both smoked heavily and drank had a 1.392 times greater risk of dying during follow-up compared with neither-users (95% CI =1.020–1.901,  $P=0.037$ ). As expected, TNM stage was the most significant predictor of OS. TNM stage III ( $P<0.001$ , HR =2.387, 95% CI =1.814–3.141) was an independent predictor of poor OS. For neither-users, either-users, and users of both heavy tobacco and alcohol, the 5-year OS rates and OS times were 57.4%, 46.4%, and 39.1% ( $P<0.05$ ) and not reached, 55.2 months, and 41.2 months ( $P<0.05$ ), respectively (Figure 2). Although a trend toward worse outcome was found, GPS 2 was not significantly associated with OS after adjusting for other covariates ( $P=0.056$ ; Table 3).

## Discussion

In this study, we found significantly worse OS in ESCC patients with a history of both heavy smoking and drinking, even after consideration of clinical data such as disease stage and GPS. Importantly, this finding was obtained in a cohort of patients who underwent radical surgery. Our results suggest that combined exposure to both heavy smoking and drinking might substantially affect tumor progression in ESCC patients treated with radical surgery. Our study included an adequately large and representative sample, comprehensively reflecting ESCC in the People's Republic of China.

To our knowledge, this is one of the largest studies worldwide investigating the influence of smoking and drinking on ESCC survival. Few studies have explored the prognostic value of smoking and drinking in ESCC. In 2008, Swedish authors reported data from a nationwide case-control study demonstrating that ESCC patients with a history of smoking (HR =2.1, 95% CI =1.0–4.4) had a worse outcome on subset analysis.<sup>17</sup> Alcohol consumption was not a significant predictor of survival in that study. However, most of the patients enrolled in the Swedish study had adenocarcinoma of the esophagus and gastric cardia and only 20% of their cases underwent esophagectomy.<sup>17</sup> In contrast, we studied ESCC patients who had all undergone radical surgery and excluded those with esophageal adenocarcinoma. Another case-control study of an Australian population found that heavy consumption of alcohol but not smoking predicted an unfavorable prognosis in ESCC patients.<sup>19</sup> In that study, only 42% of the patients underwent resection and >30% were not treated with curative intent. Moreover, the study did not provide complete clinical data for all patients. For almost 50% of the patients included, information on AJCC stage was insufficient.

In addition to reports from Western countries, there have also been studies in Eastern countries where ESCC is relatively



**Figure 1** Kaplan-Meier curves for DFS according to exposure to heavy smoking and drinking.

**Abbreviation:** DFS, disease-free survival.

**Table 2** Univariate and multivariate analyses of DFS in 488 ESCC patients

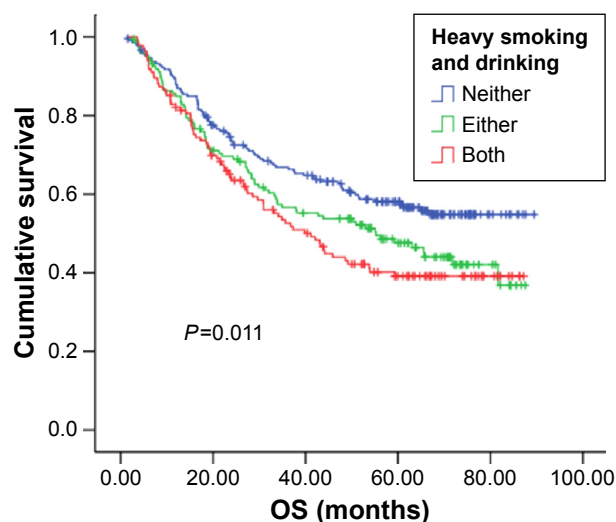
Characteristics	Median DFS	5-year DFS	Univariate		Multivariate	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Sex				0.110		
Male	37.5	40.6	I			
Female	58.5	46.9	0.796 (0.601–1.053)			
Age (years)				0.358		
<60	39.0	40.1	I			
≥60	50.2	43.9	0.896 (0.708–1.133)			
Tumor grade				0.030*		0.032*
I–II	48.6	45.6	I		I	
III	31.6	30.9	1.343 (1.029–1.752)		1.338 (1.025–1.746)	
Tumor location						
Upper	28.9	39.7	I			
Middle	43.9	42.1	0.877 (0.577–1.333)	0.539		
Lower	36.8	43.3	0.900 (0.573–1.413)	0.646		
Tumor length				0.020*		0.197
≤3 cm	50.9	45.7	I		I	
>3 cm	30.8	39.0	1.322 (1.046–1.671)		1.170 (0.922–1.484)	
TNM stage				<0.001		<0.001*
I–II	NR	55.6	I		I	
III	20.8	25.1	2.414 (1.902–3.062)		2.255 (1.754–2.897)	
Treatment				0.010*		0.609
Surgery alone	48.6	45.1	I		I	
Surgery + RT/CT	23.7	32.6	1.426 (1.088–1.869)		1.076 (0.812–1.426)	
GPS						
0	48.6	44.7	I			
1	30.8	35.3	1.283 (0.963–1.710)	0.089		
2	23.6	21.4	1.752 (0.955–3.213)	0.070		
NLR				0.131		
<2	49.7	44.7	I			
≥2	31.6	39.5	1.198 (0.948–1.513)			
Heavy smoking				0.045		
No	55.1	46.9	I			
Yes	34.7	37.5	1.272 (1.005–1.619)			
Drinking				0.041*		
No	50.8	45.9	I			
Yes	30.9	35.3	1.288 (1.010–1.643)			
Heavy smoking and drinking						
Neither	58.5	48.5	I		I	
Either	37.9	39.2	1.299 (0.982–1.720)	0.067	1.213 (0.915–1.608)	0.179
Both	30.9	35.1	1.400 (1.051–1.865)	0.022*	1.242 (0.929–1.660)	0.143

**Note:** \* $P < 0.05$ .**Abbreviations:** DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy; GPS, Glasgow Prognostic Score; NLR, neutrophil/lymphocyte ratio; TNM, Tumor-Node-Metastases.

prevalent. Shitara et al<sup>18</sup> conducted a retrospective study in a Japanese population and found that smoking history strongly predicted poor prognosis in ESCC patients; 364 cases were included in this study and the results showed that heavy smoking increased the mortality risk to 1.73 (95% CI = 1.12–2.68,  $P = 0.013$ ) compared with nonsmokers. Importantly, the effect of the interaction between heavy smoking and treatment with chemoradiotherapy on the prognosis of 195 ESCC patients was determined. No prognostic effect of heavy smoking was detected in 168 ESCC patients treated with surgery or

endoscopic mucosal resection. Alcohol drinking was also investigated in this study, but no significant findings were obtained. Wu et al<sup>20</sup> retrospectively analyzed data from 718 ESCC patients from Taiwan and discussed the prognostic effect of lifestyle factors. Habitual alcohol drinking was shown to be the strongest predictor of ESCC survival. Combined exposure to drinking, smoking, and areca chewing was an independent predictor of worse prognosis in ESCC patients. However, Wu et al's study included more cases of advanced ESCC ( $n = 506$ , 70.6%) than were included in our study and no





**Figure 2** Kaplan-Meier curves for OS according to exposure to heavy smoking and drinking.

**Abbreviation:** OS, overall survival.

information on cancer treatment was provided. In view of the ethnic and epidemiological similarity between our patients and patients of that study, we selected the same cutoff to identify drinkers. Recently, a Chinese study of 79 ESCC patients (four in stage IV) managed with primary radiotherapy reported that neither smoking nor drinking was associated with prognosis in ESCC, though any effect of smoking or drinking on prognosis might have been shadowed by the small sample size.<sup>2</sup>

In this study, combined exposure to both heavy smoking and alcohol drinking significantly increased the risk of death to 1.392 compared with neither-users. We focused on a patient population with nonmetastatic ESCC who were treated with radical esophagectomy, reflecting the real clinical entity of ESCC in the People's Republic of China. Our inclusion criteria largely reduced any potential selection bias. However, a history of combined exposure seemed not to be linked to DFS in the ESCC patients in our study. More adjuvant treatments were prescribed for alcohol drinkers ( $n=46$ , 27.9%,  $P=0.009$ ) and for heavy smokers ( $n=60$ , 24%,  $P=0.108$ ). The relatively more advanced stage of ESCC in heavy smokers and drinkers might explain this finding.

The exact mechanism by which exposure to both tobacco and alcohol leads to worse survival in ESCC remains unknown. This phenomenon is likely to occur for many reasons. First, cumulative exposure to both tobacco and alcohol impairs the individual's immune system and nutritional status, leading to a systemic inflammatory response.<sup>21–23</sup> Our data show that heavy smokers were more likely to have higher NLR at initial diagnosis ( $P<0.05$ ). A consequence of these alterations in immune function and nutritional status would be a decrease in the effectiveness of treatment and an increase in the incidence of

treatment-related complications. In addition, consumption of alcohol or nicotine can lead to molecular and genetic changes in tumor cells. Overexpression of DNA repair enzymes caused by heavy smoking has been observed in esophageal cancer, resulting in poor response to chemotherapy.<sup>24–26</sup> Smoking produces hypoxia and thus influences the radiosensitivity and promotes the angiogenesis of ESCC.<sup>27</sup> p53 mutation was reported to be more common in heavy smokers.<sup>28,29</sup> Alcohol has been found to induce a more aggressive phenotype in ESCC tumors. Coupled with genetic alterations in acetaldehyde elimination modulated by alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2), tumors develop and spread aggressively, resulting in younger age at diagnosis of ESCC.<sup>12,30</sup> Our data suggest that both heavy smoking and alcohol drinking are significantly associated with advanced clinical stage at initial diagnosis of ESCC (both  $P<0.05$ ). Furthermore, alcohol drinking was found to be associated with larger tumor size ( $>3$  cm) at baseline. We might conclude that the complex genetic/molecular changes caused by both heavy smoking and drinking promote the development of ESCC and thus affect its prognosis.<sup>15,24,25,31</sup> Finally, heavy smoking and drinking can lead to other diseases that could contribute to earlier death from ESCC,<sup>17</sup> which could be partly supported by our results. Among patients who both smoked heavily and drank, three patients died from cardiovascular diseases, five died from pulmonary diseases, and one died from chemotherapy-related toxicity. In contrast, among those who neither smoked heavily nor drank, only one patient died from cardiovascular diseases. This is a possible explanation for our finding that combined exposure was associated with OS but not DFS.

Our study has limitations. We investigated the prognostic impact of smoking and alcohol status at baseline but did not obtain sufficient information concerning the smoking and drinking behaviors of our ESCC patients. Moreover, there are other factors we should take into account, for example, continuing or stopping the use of tobacco or alcohol during treatment is a critical issue.

## Conclusion

Our results indicate that combined exposure to both heavy smoking and drinking might be predictive of poor prognosis in ESCC patients. This finding could be helpful for the management of ESCC patients with respect to their tobacco and alcohol use. Collection of detailed information on smoking and drinking should be considered in prospective studies of ESCC in the future. For ESCC patients who are both heavy smokers and drinkers, more frequent follow-up and more aggressive treatment are recommended. Our findings need to be validated in future studies and the molecular/

**Table 3** Univariate and multivariate analyses of OS in 488 ESCC patients

Characteristics	Median OS	5-year OS	Univariate		Multivariate	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Sex				0.236		
Male	55.1	48.2	I			
Female	NR	52.4	0.834 (0.617–1.126)			
Age (years)				0.376		
<60	64.9	51.2	I			
≥60	55.1	47.1	1.121 (0.871–1.443)			
Tumor grade				0.069		
I–II	66.8	51.9	I			
III	44.1	40.2	1.306 (0.979–1.741)			
Tumor location						
Upper	NR	50.1	I			
Middle	55.2	48.0	0.954 (0.599–1.518)	0.841		
Lower	81.7	53.1	0.912 (0.551–1.510)	0.720		
Tumor length				0.021*		0.301
≤3 cm	71.8	52.3	I		I	
>3 cm	43.2	46.0	1.348 (1.047–1.737)		1.146 (0.885–1.485)	
TNM stage				<0.001*		<0.001*
I–II	NR	62.4	I		I	
III	30.9	32.4	2.525 (1.949–3.270)		2.387 (1.814–3.141)	
Treatment				0.019*		0.950
Surgery alone	66.8	52.5	I		I	
Surgery + RT/CT	36.3	38.6	1.417 (1.060–1.895)		0.990 (0.729–1.346)	
GPS						
0	71.8	52.3	I		I	
I	35.6	39.6	1.393 (1.027–1.889)	0.033*	1.111 (0.812–1.521)	0.511
2	27.2	23.4	1.823 (0.963–3.449)	0.065	1.879 (0.985–3.587)	0.056
NLR				0.118		
<2	65.6	52.4	I			
≥2	48.6	46.0	1.223 (0.950–1.575)			
Heavy smoking				0.011*		
No	NR	55.7	I			
Yes	44.1	43.0	1.396 (1.081–1.802)			
Drinking				0.014*		
No	81.7	54.3	I			
Yes	41.2	39.9	1.385 (1.068–1.797)			
Heavy smoking and drinking						
Neither	NR	57.4	I		I	
Either	55.2	46.4	1.364 (1.005–1.852)	0.047*	1.301 (0.956–1.771)	0.094
Both	41.2	39.1	1.578 (1.160–2.148)	0.004*	1.392 (1.020–1.901)	0.037*

**Note:** \*P<0.05.

**Abbreviations:** OS, overall survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; NR, not reached; RT, radiotherapy; CT, chemotherapy; GPS, Glasgow Prognostic Score; NLR, neutrophil/lymphocyte ratio; TNM, Tumor-Node-Metastases.

genetic mechanism of the effect of smoking and drinking on ESCC should be further elucidated and interpreted.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Jiang JM, Zeng XJ, Chen JS, et al. Smoking and mortality from esophageal cancer in China: a large case-control study of 19,734 male esophageal cancer deaths and 104,846 living spouse controls. *Int J Cancer*. 2006;119(6):1427–1432.
- Zhang F, Han H, Wang C, et al. A retrospective study: the prognostic value of anemia, smoking and drinking in esophageal squamous cell carcinoma with primary radiotherapy. *World J Surg Oncol*. 2013;11:249.
- Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chin J Cancer*. 2012; 31(6):281–286.
- Wang SY, Mao WM, Du XH, Xu YP, Zhang SZ. The 2002 AJCC TNM classification is a better predictor of primary small cell esophageal carcinoma outcome than the VALSG staging system. *Chin J Cancer*. 2013;32(6):342–352.
- Jankova L, Dent OF, Chan C, Chapuis P, Clarke SJ. Preoperative neutrophil/lymphocyte ratio predicts overall survival but does not predict recurrence or cancer-specific survival after curative resection of node-positive colorectal cancer. *BMC Cancer*. 2013;13:442.

6. Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. *World J Surg Oncol*. 2014;12:58.
7. Miyata H, Yamasaki M, Kurokawa Y, et al. Prognostic value of an inflammation-based score in patients undergoing pre-operative chemotherapy followed by surgery for esophageal cancer. *Exp Ther Med*. 2011;2(5): 879–885.
8. Sharaiha RZ, Halazun KJ, Mirza F, et al. Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol*. 2011;18(12): 3362–3369.
9. Feng JF, Huang Y, Liu JS. Combination of neutrophil lymphocyte ratio and platelet lymphocyte ratio is a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma. *Oncotargets Ther*. 2013;6:1605–1612.
10. Feng JF, Zhao Q, Chen QX. Prognostic significance of Glasgow prognostic score in patients undergoing esophagectomy for esophageal squamous cell carcinoma. *Saudi J Gastroenterol*. 2014;20(1):48–53.
11. Vioque J, Barber X, Bolumar F, et al. Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC Cancer*. 2008;8:221.
12. Radojicic J, Zaravinos A, Spandidos DA. HPV, KRAS mutations, alcohol consumption and tobacco smoking effects on esophageal squamous-cell carcinoma carcinogenesis. *Int J Biol Markers*. 2012;27(1):1–12.
13. Pandeya N, Olsen CM, Whiteman DC. Sex differences in the proportion of esophageal squamous cell carcinoma cases attributable to tobacco smoking and alcohol consumption. *Cancer Epidemiol*. 2013;37(5): 579–584.
14. Tai SY, Wu IC, Wu DC, et al. Cigarette smoking and alcohol drinking and esophageal cancer risk in Taiwanese women. *World J Gastroenterol*. 2010;16(12):1518–1521.
15. Yaegashi Y, Onoda T, Morioka S, et al. Joint effects of smoking and alcohol drinking on esophageal cancer mortality in Japanese men: findings from the Japan collaborative cohort study. *Asian Pac J Cancer Prev*. 2014;15(2):1023–1029.
16. Lee CH, Wu DC, Lee JM, et al. Carcinogenic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. *Eur J Cancer*. 2007;43(7):1188–1199.
17. Sundelof M, Lagergren J, Ye W. Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden. *Eur J Cancer*. 2008;44(11):1566–1571.
18. Shitara K, Matsuo K, Hatooka S, et al. Heavy smoking history interacts with chemoradiotherapy for esophageal cancer prognosis: a retrospective study. *Cancer Sci*. 2010;101(4):1001–1006.
19. Thrift AP, Nagle CM, Fahey PP, et al. The influence of prediagnostic demographic and lifestyle factors on esophageal squamous cell carcinoma survival. *Int J Cancer*. 2012;131(5):E759–E768.
20. Wu IC, Wu CC, Lu CY, et al. Substance use (alcohol, areca nut and cigarette) is associated with poor prognosis of esophageal squamous cell carcinoma. *PLoS One*. 2013;8(2):e55834.
21. Wang AX, Xu B, Tong N, et al. Meta-analysis confirms that a common G/C variant in the pre-miR-146a gene contributes to cancer susceptibility and that ethnicity, gender and smoking status are risk factors. *Genet Mol Res*. 2012;11(3):3051–3062.
22. Walser T, Cui X, Yanagawa J, et al. Smoking and lung cancer: the role of inflammation. *Proc Am Thorac Soc*. 2008;5(8):811–815.
23. Malfertheiner P, Schutte K. Smoking – a trigger for chronic inflammation and cancer development in the pancreas. *Am J Gastroenterol*. 2006; 101(1):160–162.
24. Nozoe T, Korenaga D, Kabashima A, Sugimachi K. Smoking-related increase of O(6)-methylguanine-DNA methyltransferase expression in squamous cell carcinoma of the esophagus. *Cancer Lett*. 2002;184(1): 49–55.
25. Ohba T, Kometani T, Shoji F, et al. Expression of an X-family DNA polymerase, pol lambda, in the respiratory epithelium of non-small cell lung cancer patients with habitual smoking. *Mutat Res*. 2009; 677(1–2):66–71.
26. Hwang IG, Ahn MJ, Park BB, et al. ERCC1 expression as a prognostic marker in N2(+) non-small-cell lung cancer patients treated with platinum-based neoadjuvant concurrent chemoradiotherapy. *Cancer*. 2008;113(6): 1379–1386.
27. Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma – a prospective study. *Radiother Oncol*. 2012;103(1): 38–44.
28. Taghavi N, Biramijamal F, Sotoudeh M, et al. Association of p53/p21 expression with cigarette smoking and prognosis in esophageal squamous cell carcinoma patients. *World J Gastroenterol*. 2010;16(39): 4958–4967.
29. Putz A, Hartmann AA, Fontes PR, et al. TP53 mutation pattern of esophageal squamous cell carcinomas in a high risk area (Southern Brazil): role of life style factors. *Int J Cancer*. 2002;98(1):99–105.
30. Lee CH, Wu DC, Wu IC, et al. Genetic modulation of ADH1B and ALDH2 polymorphisms with regard to alcohol and tobacco consumption for younger aged esophageal squamous cell carcinoma diagnosis. *Int J Cancer*. 2009;125(5):1134–1142.
31. Wang AH, Sun CS, Li LS, Huang JY, Chen QS. Relationship of tobacco smoking CYP1A1 GSTM1 gene polymorphism and esophageal cancer in Xi'an. *World J Gastroenterol*. 2002;8(1):49–53.

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