


ORIGINAL ARTICLE

Propensity score analysis exploring the impact of smoking and drinking on the prognosis of patients with oral cancer

Xiaodan Bao BS^{1,2} | Fengqiong Liu PhD^{1,2} | Qing Chen BS^{1,2} | Lin Chen BS^{1,2} |
Jing Lin BS^{1,2} | Fa Chen PhD^{1,2} | Jing Wang MD³ | Yu Qiu MD⁴ |
Bin Shi PhD⁴ | Lizhen Pan BS⁴ | Lisong Lin PhD⁴ | Baochang He PhD^{1,2} 

¹Department of Epidemiology and Health Statistics, Fujian Provincial Key Laboratory of Environment Factors and Cancer, School of Public Health, Fujian Medical University, Fujian, China

²Key Laboratory of Ministry of Education for Gastrointestinal Cancer, Fujian Key Laboratory of Tumor Microbiology, Fujian Medical University, Fujian, China

³Laboratory Center, The Major Subject of Environment and Health of Fujian Key Universities, School of Public Health, Fujian Medical University, Fujian, China

⁴Department of Oral and Maxillofacial Surgery, The First Affiliated Hospital of Fujian Medical University, Fujian, China

Correspondence

Baochang He, Department of Epidemiology and Health Statistic, School of Public Health, Fujian Medical University, 1 Xueyuan Road, Fuzhou 350108, China.
Email: prof_hbc@163.com

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Abstract

Background: To explore the effect of smoking and drinking on survival of patients with oral cancer by comparing the characteristics and survival of nonsmoking and nondrinking (NSND) patients in contrast to smoking and/or drinking (SD) patients.

Methods: This prospective study including 1165 patients with oral cancer was conducted in Fujian, China from January 2005 to January 2019. The patients were categorized to two groups, the NSND group and SD group. We compared overall survival and disease-specific survival between the two groups using the Kaplan-Meier method and Cox proportional hazards regression before and after propensity score matching (PSM) to explore the effect of smoking and drinking on the prognosis of patients with oral cancer.

Results: NSND patients accounted for 55.45% (646 patients) of all the patients with oral cancer. SD patients with oral cancer tended to be older and mainly are male (98.46%) and with more advanced disease status. There are trends toward both higher risk of all-cause death (HR = 1.678; 95% CI: 1.086-2.594) and oral cancer specific death (HR = 1.632; 95% CI: 1.044-2.552) in SD patients with oral cancer before PSM. After PSM, the association is still significant, with adjusted HR of 1.897 (95% CI: 1.138-3.165) for all-cause death and adjusted HR of 1.764 (95% CI: 1.043-2.983) for oral cancer-specific

Xiaodan Bao and Fengqiong Liu contributed equally to this study.

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death. Additionally, PSM can improve the HR value and result in a stronger association.

Conclusions: Social and clinical characteristics of NSND patients differed from SD patients with oral cancer. SD patients with oral cancer have higher all-cause mortality and oral cancer-specific mortality than NSND patients.

KEYWORDS

all-cause mortality, nondrinking, nonsmoking, oral cancer, oral cancer-specific mortality

1 | INTRODUCTION

Oral cancer is malignant tumor seriously endangering quality of life and leading to significant mortality.¹⁻³ According to recent data from the GLOBOCAN 2018, the age-standardized mortality of oral cancer was 2.8 of 100000 for male and 1.2 of 100000 for female.⁴

It has been well established that tobacco smoking and alcohol consumption are major risk factors for the development of oral cancer. In addition, the combination of tobacco smoking and alcohol consumption has a synergistic effect on oral cancer.⁵⁻⁹ In recent years, nonsmoking and nondrinking (NSND) patients have been identified as a distinct and growing subset of oral cancer. Nevertheless, the survival outcomes of this specific group patients have been largely neglected.

Results from the current few studies have been controversial, with some studies pointing out both smoking and drinking were linked to a higher risk of death in oral cancer,¹⁰⁻¹² while other studies showed that the prognosis of NSND oral squamous cell carcinoma (OSCC) patients is no different from that of smoking and/or drinking (SD) patients,¹³ or even worse.¹⁴ In fact, data has showed that NSND patients with oral cancer are younger and more likely to be female and with earlier disease stages.^{13,14} In addition, previous studies have reported that smokers have a higher prevalence of genetic mutations than nonsmokers.^{15,16} Differences in the distribution of these confounders may lead to the controversial results observed in prognosis of NSND patients. Propensity score matching (PSM) could equalize the initially differences between two groups and increase the reliability of results. However, thus far, no prospective study about the prognosis of NSND using PSM has been reported.

The objective of this study is to compare the social and clinical characteristics, as well as the prognosis of

NSND and SD patients with oral cancer from southeast China by using PSM.

2 | PATIENTS (OR SUBJECTS) AND METHODS

2.1 | Study population

A total of 1165 patients with oral cancer were consecutively recruited from The First Affiliated Hospital of Fujian Medical University from January 2005 to August 2018. All patients were histologically confirmed primary oral cancer cases. As described previously,¹⁷ all patients were Chinese Han population and resided in Fujian Province for more than 10 years. Patients who with recurrent oral cancer or distant metastasized cancer were excluded. This prospective study was approved by the Institutional Review Board (IRB) of Fujian Medical University (Fuzhou, China) and performed in line with the ethical standards described in the Declaration of Helsinki.

2.2 | Data collection

Tumor characteristics (TNM stage, pathological grading, pathological type, etc.) were retrieved from patients' medical records. Demographic characteristics (occupation, education level, origin, etc.) and lifestyle habits (including smoking and drinking status) data were collected via interview-based structured and self-reported questionnaires distributed at diagnosis. Details of the treatment have been provided in previous reports.¹⁸ Mortality data were sourced from telephone interview with 6-month intervals or hospital patient attendance records. We also verify the death of patients through national death surveillance system. The cause of death was recorded in the Resident Medical Certificate of Death Form which is

issued by physician. The follow-up was consistent until January 2019.

2.3 | Definition of variables

This study adopted a uniform InterCHANGE lifestyle questionnaire, which was compiled by the university of Utah and the institute of oncology, Chinese academy of medical sciences, united with famous epidemiologists in China and the actual situation in China. Subjects were asked to report the total number of years smoking and the average cigarettes consumption level per day. As for alcohol drinking, information about average number of drinks per week and total number of years drinking was collected.

All patients were staged using the AJCC staging system, version 7, 2010. The AJCC staging system before 2010 was slightly differ from systems used after 2010, so we updated the disease staging information before 2010 using clinical pathological reports according to the new AJCC staging system. All-cause mortality was defined as the death from any cause. And the second outcome of interest was death from oral cancer. The occupational classification was determined by the professional classification of the People's Republic of China. Farmers refer to agricultural, forestry, animal husbandry, and fishery production personnel; workers refer to production and transportation operators. Office workers refer to staff of the government or the principal of a group or a unit, professional and technical personnel, clerical and related personnel. Illiteracy refers to those who have never been to school and cannot read. The classification of urban or rural areas was determined according to the administrative division of China. The origin is derived from household registry information that includes the birth place and residence of the participant.

2.4 | Statistical analysis

The cumulative smoking exposure was calculated as pack-years of smoking which was the product of the number of packs consumed per day and number of years of smoking. Sensitivity analysis was conducted with regard to smoking and alcohol consumption to define appropriate threshold for smoking and drinking, and to define the SD and NSND group.

Chi-square test was used to compare demographic characteristics between NSND group and SD group. The survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate Cox regression models were used to

assess the effects of smoking and drinking. A propensity score (PS) applying the method of nearest neighbor matching within a specified caliper distance (calipers of width equal to 0.02) without replacement was used to assess the effects of smoking and drinking, in order to minimize the potential confounding bias which could influence the results. The NSND group was 1:1 matched on age, gender, occupation, education level, residence, BMI, TNM stage, and pathological type with SD group. All statistical analyses were performed with the R software version 3.6.1. A *P* value of <.05 was taken to be significant.

3 | RESULTS

Sensitivity analysis was conducted using different threshold of smoking, the effect of smoking was more significant when the cutoff point for smoking was 10 pack years or 20 pack years compared with 100 cigarettes in life time especially for oral cancer specific mortality (Table 1). While the effect of drinking was more significant when the cutoff point for drinking was at least seven drinks per week continuously for at least 1 year compared with at least one drink a week continuously for at least 6 months (Table 1). We also analyzed the prognosis of patients according to different levels smoking duration and smoking frequency (Table S1), and found that longer duration and higher consumption frequency is positively related to worse prognosis. In addition to smoking, we also explored the relationship between different alcohol drinking duration and frequency and prognosis of oral cancer, and found that patients who drank more than seven times a week had significantly poorer overall survival (Table S1).

Based on the results of sensitivity analysis, smokers (ex and current smoker) were defined as those who had smoked at least 10 pack years cigarettes in their lives. Patients were considered to be drinkers (ex and current drinker) if they consumed alcohol at least seven drinks per week continuously for at least 1 year. Patients were categorized as NSND or SD. A total of 646 patients (55.45%) were identified as NSND from 1165 patients with oral cancer, while SD group patients represent approximately 44.55% (519) of the oral cancer population. A peak at 60 to 70 years was observed in the NSND group, while a peak at 50 to 60 years was seen in SD group (Figure 1). Moreover, we observed extremely difference in sex distribution between NSND and SD groups (Figure 1). The SD group was predominantly male (98.46%), while the NSND group was dominated by female patients (65.63%). NSND group has higher proportion of patients with BMI ≥ 24 kg/m² than SD group. In

TABLE 1 Survival analysis for SD vs NSND patients with oral cancer based on different threshold of smoking and drinking classification in full cohort

	Number of patients (%)	All-cause mortality HR (95%CI)	Oral cancer specific mortality HR (95%CI)
Threshold of smoking			
100 cigarettes ^a			
No	620 (53.22)	1.000	1.000
Yes	545 (46.78)	1.586 (1.001, 2.512)	1.564 (0.975, 2.507)
10 pack years ^b			
No	680 (58.37)	1.000	1.000
Yes	485 (41.63)	1.842 (1.195, 2.840)	1.782 (1.143, 2.777)
20 pack years ^c			
No	731 (62.75)	1.000	1.000
Yes	434 (37.25)	1.743 (1.166, 2.604)	1.666 (1.104, 2.513)
Threshold of drinking			
>1 times/week ^d			
No	756 (64.89)	1.000	1.000
Yes	408 (35.01)	1.029 (0.724, 1.462)	1.048 (0.729, 1.508)
>7 times/week ^e			
No	937 (80.43)	1.000	1.000
Yes	228 (19.57)	1.463 (1.064, 2.011)	1.317 (0.905, 1.915)

Note: All adjusted for age, gender, occupation, education level, residence, BMI, TNM stage, pathological grading and pathological type, pathological grading and adjuvant therapy.

^aSmokers (ex and current smoker) were defined as those who had smoked at least 100 cigarettes in their lives.

^bSmokers (ex and current smoker) were defined as those who had smoked at least 10 pack years cigarettes in their lives.

^cSmokers (ex and current smoker) were defined as those who had smoked at least 20 pack years cigarettes in their lives.

^dDrinkers (ex and current smoker) were defined as at least one drink a week continuously for at least 6 months.

^eDrinkers (ex and current smoker) were defined as at least seven drink per week continuously for at least 1 year.

addition, NSND patients were more likely to present at earlier disease stage, with 44.16% in I and II stages, 55.83% at T1 and T2 classifications; however, no difference was observed in N classification. Details of demographics and clinical characteristics of all patients were listed in Table 2.

Before PSM, log-rank test showed that patients with SD had a significantly higher all-cause mortality ($P = .002$, Figure 2) and oral cancer-specific mortality ($P = .010$, Figure 2) than those with NSND. The variables that were not equally distributed between the groups and are potential confounders (age, gender, occupation, education level, residence, BMI, TNM stage, pathological type, pathological grading, and adjuvant therapy) were included and the enter method were used to develop the cox regression model models to adjust the potential confounding effect of those factors.

There are three cox regression model used: (a) In the crude model, no confounding factors were adjusted; (b) in the second cox model, only gender and age were

adjusted; and (c) in the full model, confounding factors such as age, gender, occupation, education level, residence, BMI, TNM stage, pathological type, pathological grading, and adjuvant therapy were adjusted. After fully adjustment of potential confounders, cox regression analysis showed that SD patients still had an increased risk of all-cause mortality ($HR: 1.678$, 95% $CI: 1.086-2.594$) and oral cancer specific mortality ($HR: 1.632$, 95% $CI: 1.044-2.552$) compared with the NSND group (Table 4).

PSM was performed in term of age, gender, occupation, education level, residence, BMI, TNM stage, and pathological type, since the distribution of these factors was unbalanced between SD group and NSND group. Out of 1165 patients, 185 NSND and 185 SD patients were selected, details of demographics and clinical characteristics of all patients were listed in Table 3. After PSM, higher all-cause mortality was still observed in patients with SD compared to those with NSND in both log rank test ($P = .003$, Figure 2) and cox regression analysis (adjusted $HR: 1.897$, 95% $CI: 1.138-3.165$). Similarly,

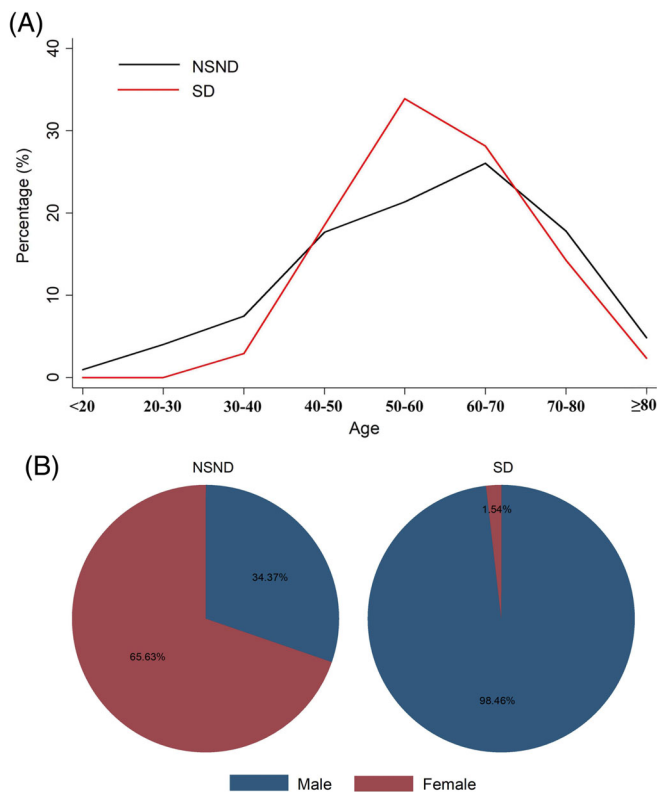


FIGURE 1 A, Age distribution of smoking and/or drinking (SD) patients compared to nonsmoker nondrinkers (NSND) patients. B, Sex distribution of SD patients compared to NSND patients [Color figure can be viewed at wileyonlinelibrary.com]

difference of oral cancer specific mortality was observed between NSND and SD patient in log rank test ($P = .013$, Figure 2) and cox regression (adjusted HR : 1.764, 95% CI : 1.043-2.983). Additionally, PSM can improve the HR value of both all-cause mortality (1.897 vs 1.678) and oral cancer specific mortality (1.764 vs 1.632) and enhance significance of association compared with the results of unmatching (Table 4).

4 | DISCUSSION

Oral cancer is traditionally a disease dominated by male smokers and drinkers. Our results showed that NSND patients accounted for 55.45% in patients with oral cancer, which was higher than the 20%- to 30% reported in the literatures.^{13,14,19} Compared to other studies in which 30% to 50% of NSND patients with oral cancer were female,^{20,21} our study population had a higher proportion of female (65.63%) in NSND patients. In general, the rates of smoking or drinking are lower for women in the southeastern China. Therefore, these findings indicate that there may be other important risk factors for oral cancer in the southeastern China besides smoking and

drinking, and more attention should be paid to the increasing NSND patient population.

Our study also showed that the average age of NSND patients was about 10 years older compared with SD patients, similar patterns were also repeated reported in numerous studies.^{13,14,21} This phenomenon suggested that tobacco and alcohol exposure may lead to development of oral cancer 10 years earlier than the non-exposure population. Although NSND patients have older age than SD patients, the prognosis of NSND is better than SD patients in terms of all-cause mortality, which indicated the protective effect of NSND on the population.

In addition to gender and age, data showed that NSND patients were less advanced than SD patients with oral cancer in TNM stage and pT classification. And patients in the NSND group had better nutritional status ($BMI \geq 24 \text{ kg/m}^2$ accounted for 27.40% in NSND group and 19.08% in SD group, respectively), which may partly explain the better prognosis observed in NSND group, since a large number of studies confirmed that patients with poor nutritional status may be more intolerant of the side effects of therapy and have adverse survival outcomes.^{22,23}

Largely owing to the differed distribution of important social and clinical relevant variables between the SD group and the NSND group, the prognosis regarding NSND has been controversial.¹⁰⁻¹⁴ Hence, we applied PSM, which is a matching method that could equalize the initially differences thus substantially decrease the bias in order to make a more reasonable comparison between groups in our study. This method was first proposed by Rosenbaum and Rubin in 1983²⁴ and is becoming more and more widely used.²⁵⁻²⁸ In our study, PSM method was adopted to make the SD group and NSND group match in many social and clinical characteristics including age, gender, occupation, education level, residence, BMI, TNM stage, and pathological type, and we found that the survival outcome of SD group was worse than that of NSND group in both before and after matching analysis. However, PSM can improve the HR value and enhance significance of association compared with results of unmatching, which validated the role of smoking and drinking in prognosis of oral cancer, and at the same time verified the potential value of PSM method.

Several limitations should be noticed when interpreting the results of this study. First, misclassification may occur because drinking and smoking are self-reported. Second, we only evaluated the prognostic value of the smoking and drinking status of patients with oral cancer at pretreatment. Hence, future studies are needed to collect information of posttreatment smoking and drinking status. Finally, this study is a single-center study

TABLE 2 Demographics of the patients in the SD group vs the NSND group before propensity score matching (N = 1165)

Variables	NSND (646) No. of patients (%)N	SD (519) No. of patients (%)N (%)	P
Sex			<.001
Male	222 (34.37)	511 (98.46)	
Female	424 (65.63)	8 (1.54)	
Age (years)			.001
<50	194 (30.03)	111 (21.39)	
≥50	452 (69.97)	408 (78.61)	
Occupation			<.001
Farmer	77 (12.11)	120 (23.21)	
Worker	353 (55.50)	230 (44.49)	
Office worker and other	206 (32.39)	167 (32.30)	
Education level			<.001
Illiteracy	101 (15.64)	26 (5.01)	
Primary-middle school	371 (57.43)	378 (72.83)	
High school and above	174 (26.93)	115 (22.16)	
Origin			.031
Urban area	349 (54.02)	313 (60.31)	
Rural area	297 (45.98)	206 (39.69)	
BMI (kg/m ²)			.002
18.5-23.9	394 (60.99)	340 (65.51)	
<18.5	75 (11.61)	80 (15.41)	
≥24	177 (27.40)	99 (19.08)	
TNM Stage			.001
I	112 (19.55)	54 (11.46)	
II	141 (24.61)	108 (22.93)	
III	106 (18.50)	84 (17.83)	
IV	214 (37.35)	225 (47.78)	
pT classification			<.001
T ₁	128 (22.61)	68 (14.38)	
T ₂	188 (33.22)	140 (29.60)	
T ₃	81 (14.31)	76 (16.07)	
T ₄	169 (29.86)	189 (39.95)	
pN classification			.529
N ₀	403 (70.70)	313 (66.74)	
N ₁	77 (13.51)	67 (14.29)	
N ₂	86 (15.09)	85 (18.12)	
N ₃	4 (0.70)	4 (0.85)	
Pathological grading			.887
Well	103 (21.73)	86 (20.67)	
Moderate	123 (25.95)	113 (27.16)	
Poor	248 (52.32)	217 (52.17)	
Pathological type			<.001
Squamous cell carcinoma	504 (78.63)	448 (86.65)	
Adenocarcinoma	137 (21.37)	69 (13.35)	

(Continues)

TABLE 2 (Continued)

Variables	NSND (646) No. of patients (%)N	SD (519) No. of patients (%)N (%)	P
Family history of cancer			.749
No	541 (83.75)	431 (83.04)	
Yes	105 (16.25)	88 (16.96)	
Adjuvant therapy			.323
No	324 (53.47)	248 (49.80)	
RT	101 (16.67)	82 (16.47)	
CT	64 (10.56)	70 (14.06)	
CRT	117 (19.30)	98 (19.67)	
Hypertension			.153
No	473 (73.22)	399 (76.88)	
Yes	173 (26.78)	120 (23.12)	
Diabetes			.126
No	578 (89.47)	478 (92.10)	
Yes	68 (10.53)	41 (7.90)	

Abbreviations: BMI, body mass index; CT, chemotherapy; CRT, chemoradiotherapy; NSND, nonsmoking and nondrinking; RT, radiotherapy; SD, smoking and/or drinking.

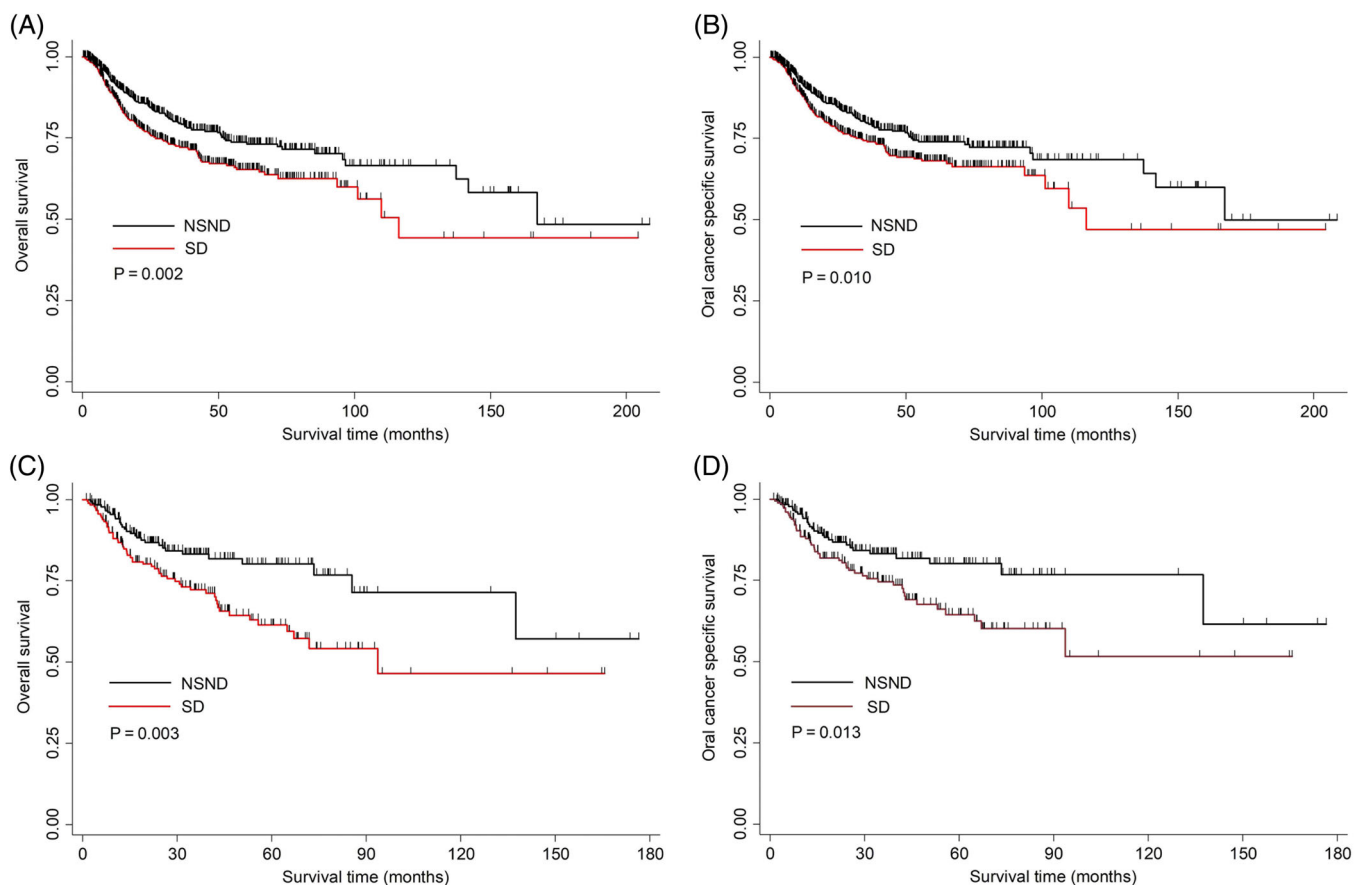


FIGURE 2 A, Overall survival rates of smoking and/or drinking (SD) patients and nonsmoker nondrinkers (NSND) patients before propensity score matching. B, Oral cancer specific survival rates of SD patients and NSND patients before propensity score matching. C, Overall survival rates of SD patients and NSND patients after propensity score matching. D, Oral cancer-specific survival rates of SD patients and NSND patients after propensity score matching [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Demographics in the SD group vs the NSND group after propensity score matching (N = 370)

Variables	NSND (185) No. of patients (%)	SD (185) No. of patients (%)	P
Sex			1.000
Male	179 (96.76)	179 (96.76)	
Female	6 (3.24)	6 (3.24)	
Age (years)			.051
<50	62 (33.51)	45 (24.32)	
≥50	123 (66.49)	140 (75.68)	
Occupation			.990
Farmer	32 (17.30)	31 (16.76)	
Worker	102 (55.14)	103 (55.68)	
Office worker and other	51 (27.57)	51 (27.57)	
Education level			.568
Illiteracy	11 (5.95)	12 (6.49)	
Primary-middle school	96 (51.89)	105 (56.76)	
High school and above	78 (42.16)	68 (36.76)	
Origin			.298
Urban area	91 (49.19)	101 (54.59)	
Rural area	94 (50.81)	84 (45.41)	
BMI (kg/m ²)			.569
18.5–23.9	116 (51.56)	106 (20.50)	
<18.5	16 (7.11)	18 (3.48)	
≥24	53	61 (11.80)	
TNM Stage			.136
I	27 (14.59)	41 (22.16)	
II	44 (23.79)	30 (16.22)	
III	35 (18.92)	34 (18.38)	
IV	79 (42.70)	80 (43.24)	
pT classification			.055
T ₁	30 (16.48)	44 (24.04)	
T ₂	58 (31.87)	37 (20.22)	
T ₃	29 (15.93)	31 (16.94)	
T ₄	65 (35.72)	71 (38.80)	
pN classification			.629
N ₀	122 (66.67)	129 (70.10)	
N ₁	25 (13.66)	28 (15.22)	
N ₂	34 (18.58)	25 (13.59)	
N ₃	2 (1.09)	2 (1.09)	
Pathological grading			.258
Well	34 (24.11)	25 (16.89)	
Moderate	39 (27.66)	40 (27.03)	
Poor	68 (48.23)	83 (56.08)	
Pathological type			.719
Squamous cell carcinoma	154 (84.62)	159 (85.95)	
Adenocarcinoma	28 (15.38)	26 (14.05)	

(Continues)

TABLE 3 (Continued)

Variables	NSND (185) No. of patients (%)	SD (185) No. of patients (%)	N (%)	P
Family history of cancer				1.000
No	148 (80.00)	148 (80.00)		
Yes	37 (20.00)	37 (20.00)		
Adjuvant therapy				.623
No	99 (56.25)	90 (50.28)		
RT	23 (13.07)	28 (15.64)		
CT	18 (10.23)	24 (13.41)		
CRT	36 (20.45)	37 (20.67)		
Hypertension				1.000
No	136 (73.51)	136 (73.51)		
Yes	49 (26.49)	49 (26.49)		
Diabetes				.459
No	171 (92.43)	167 (90.27)		
Yes	14 (7.57)	18 (9.73)		

Abbreviations: BMI, body mass index; CT, chemotherapy; CRT, chemoradiotherapy; NSND, nonsmoking and nondrinking; RT, radiotherapy; SD, smoking and/or drinking.

TABLE 4 Survival analysis for SD vs NSND patients with oral cancer

	Number of censored (%)	Number of death (%)	Log rank P	Crude model	Age- and sex-adjusted model ^a	Fully adjusted model ^b
Before propensity score matching						
All-cause mortality			0.002			
NSND	519 (57.80)	127 (47.57)		1.000	1.000	1.000
SD	379 (42.20)	140 (52.43)		1.474 (1.159, 1.875)	1.722 (1.206, 2.459)	1.678 (1.086,2.594)
Oral cancer specific mortality			0.010			
NSND	522 (57.17)	124 (49.21)		1.000	1.000	1.000
SD	391 (42.83)	128 (50.79)		1.380 (1.078,1.768)	1.623 (1.127,2.337)	1.632 (1.044,2.552)
After propensity score matching						
All-cause mortality			0.003			
NSND	155 (54.58)	30 (34.88)		1.000	1.000	1.000
SD	129 (45.42)	56 (65.12)		1.933 (1.240,3.013)	2.010 (1.288,3.137)	1.897 (1.138,3.165)
Oral cancer specific mortality			0.013			
NSND	156 (53.61)	29 (36.71)		1.000	1.000	1.000
SD	135 (46.39)	50 (63.29)		1.778 (1.125,2.811)	1.844 (1.165,2.918)	1.764 (1.043,2.983)

Abbreviation: NSND: nonsmoking and nondrinking; SD: smoking and/or drinking.

^aAdjusted for age, gender.

^bAdjusted for age, gender, occupation, education level, residence, BMI, TNM stage, pathological type, pathological grading and adjuvant therapy.

that may limit generalization to other populations to some extent. Therefore, future multicenter research will be necessary.

In conclusion, our study showed that nearly a half of patients with oral cancer are NSND patients in China. The overall survival and disease specific survival of

NSND patients are better than SD patients after PS matching for critical social and clinical characteristics. In other words, smoking and drinking provide any additional prognostic information beyond the traditional prognostic factors in patients with oral cancer.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

B.H. constructed the study design. X.B. and F.L. contributed to data interpretation, and manuscript drafting. J.W. and F.C. contributed to statistical analysis. L.C., C.Q., J.L., and L.P. participated in the clinical investigation, contributed to the epidemiological data collection. Y.Q., L.L., and B.S. revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Review Board (IRB) of Fujian Medical University (2011053). Written informed consent was obtained from all individual participants included in the study.

ORCID

Baochang He  <https://orcid.org/0000-0002-5357-2171>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Supplement table1 Adjusted hazard ratios, and 95% confidence intervals for tobacco smoking and alcohol drinking and oral cancer in full cohort

	All-cause mortality	Oral cancer specific mortality
	<i>HR (95%CI)</i>	<i>HR (95%CI)</i>
Tobacco smoking duration		
Never	1.000	1.000
0-45 years	1.427(0.885,2.302)	1.382(0.845,2.261)
>45 years	2.280(1.263,4.116)	2.358(1.288,4.317)
Tobacco smoking frequency		
Never	1.000	1.000
0-10cigarettes/day	0.909(0.343,2.413)	0.977(0.366,2.603)
>10cigarettes/day	1.654(1.037,2.636)	1.617(1.002,2.612)
Alcohol drinking duration		
Never	1.000	1.000
0-35 years	0.956(0.630,1.450)	0.976(0.635,1.499)
>35 years	1.136(0.732,1.764)	1.145(0.726,1.804)
Alcohol drinking frequency		
Never	1.000	1.000
0-7 times/week	0.937(0.611,1.438)	0.848(0.518,1.390)
>7 times/week	1.400(1.021,1.979)	1.231(0.822,1.844)

Abbreviation: All adjusted for age, gender, occupation, education level, residence, BMI, TNM stage, pathological grading and pathological type, pathological grading and adjuvant therapy