Lifestyle factors and long-term survival of gastric cancer patients: a large bidirectional cohort study from China.

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Abstract

Background: Lifestyle factors such as body mass index (BMI), alcohol drinking, and cigarette smoking, are likely to profoundly impact the prognosis of gastric cancer, but evidence has been inconsistent.

Methods: Patients with gastric cancer were identified from the China National Cancer Center Gastric Cancer Database (NCCGCDB) 1998-2018. Survival analysis performed via Kaplan-Meier estimates and Cox proportional hazards models.

Results: In this study, we reviewed 18 441 cases of gastric cancer patients. Individuals who were overweight or obese was associated with positive smoking and drinking history ($P=0.002$ and $P<0.001$, respectively). Current smokers are more likely to be current alcohol drinkers (61.3% vs. 10.1% vs. 43.2% for current, never, and former smokers, respectively, $P<0.001$). Multivariable results indicated that BMI at diagnosis had no significant effect on prognosis. In gastrectomy patients, factors independently associated with poor survival include older age ($HR=1.20$, 95% CI: 1.05-1.38, $P=0.001$), any weight loss ($P<0.001$), smoking history more than 30 years ($HR=1.14$, 95% CI: 1.04-1.24, $P=0.004$), and increasing pTNM stage ($P<0.001$).

Conclusion: In conclusion, this study of gastric cancer patients has examined the association of lifestyle factors above with long-term prognosis. Among the patients overall, weight loss (both 0-10% and >10% groups), but not BMI values at diagnosis, was related to survival results. For other factors, smoking history of more than 30 years conferred a worse prognosis for only gastrectomy patients. Extensive efforts are needed to elucidate mechanisms targeting the complex effects of lifestyles factors.

Background

Gastric cancer is the third leading cause of cancer-related mortality and the sixth most common cancer globally [1]. More than 70% of new cases occur in developing countries, and half of the world's total occur in Eastern Asia, mainly in China [2]. As the patient population grows, factors contributing to improved or adverse survival are becoming a focus of increasing interest.

Obesity defined as high BMI results from the expansion of white adipose tissue, commonly referred to as fat. To date, evidence for the association between body mass index (BMI) and prognosis in gastric cancer patients has been inconsistent. Some studies [3–8] have reported that being overweight was associated with improved long-term survival for gastric cancer patients with gastrectomy, whereas other results [9–16] informed that BMI was not a prognostic factor. Three studies [17–19] even expressed poor survival of gastric cancer patients with higher BMI. However, some previous studies have used coarse categories, such as BMI <25.0 and ≥ 25 [15, 20–22]. Furthermore, these results may not apply to Chinese population owing to the different BMI categorization criteria for the Asian, therefore the association between BMI and prognosis has remained unclear in China.

Similarly, the prognostic effects of alcohol drinking and smoking status at diagnosis for gastric cancer are also contradictory, although cigarette smoking was known to be associated with stomach cancer risk [23, 24].

Alcohol drinking at diagnosis was reported to decrease survival in patients with gastric cancer in some studies [25, 26], while several studies [27–30] did not confirm this finding. Some studies [28, 29, 31, 32] have shown a positive association between smoking and overall survival from gastric cancer, while other studies [25, 27, 33]

have found that smoking status was not statistically related to prognosis. Deficiency, most published studies, especially prospective studies, have not adjusted for potentially significant covariates such as gastrectomy.

As such, we conducted a single-centre, large-scale bidirectional cohort study from China National Cancer Center to investigate on the three major lifestyle factors mentioned above - BMI, alcohol drinking, and smoking - and attempted to clarify the association of these factors with the overall survival of patients with gastric cancer.

Methods

Patient Population

All patients' records were abstracted from the China National Cancer Center Gastric Cancer Database (NCCGCDB). The NCCGCDB was a clinical gastric cancer database based on a huge bidirectional cohort, which sourced from China National Cancer Center, a single but large-volume institution whose patients from all around China 1998 to 2018. After a histology diagnosis confirmed by pathology of gastric cancer, 18 441 gastric cancer patients included finally. The median follow-up of the gastric cancer patients were 62.7 ± 3.5 months until December 2018. 1818 patients were lost during our follow-up with a loss rate of 9.86%. The geographical locations of these gastric cancer patients can be found in Figure 1.

Statistical Analyses

BMI at diagnosis was calculated as weight at diagnosis (kg) of gastric cancer divided by the square of height (m^2). For the analysis of BMI according to the Asian criteria, patients were stratified according to the following BMI categories: underweight ($<18.5 \text{ kg}/m^2$), healthy weight (≥ 18.5 to $<23 \text{ kg}/m^2$), overweight (≥ 23 to $<27.5 \text{ kg}/m^2$) and obese ($\geq 27.5 \text{ kg}/m^2$).

Other lifestyle variables related to cigarette smoking included smoking status (never, current, and former smokers), time since quitting smoking (1–9 and ≥ 10 years), number of cigarettes per day (≤ 20 , 21–39, and ≥ 40), and duration of smoking (1–29 and ≥ 30 years). For alcohol drinking, drinking status (never, current, and former drinkers) and amount of alcohol consumed per day (light drinkers, $<15.6\text{g}$; moderate drinkers, $\geq 15.0\text{g}$ to $<53.5\text{g}$; and heavy drinkers, $\geq 53.5\text{g}$) included. Subjects who quit smoking or drinking within one year before the present admission were regarded as current smokers or drinkers, respectively.

Categorical variables were compared using the Chi-squared test, and continuous variables were analyzed by the Student's t-test. Survival curves were plotted for total patients, no-surgery, gastrectomy and only curative gastrectomy groups, respectively, using the Kaplan-Meier method and compared statistically using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to estimate the risk of death by employing the multivariate Cox proportional hazards models with adjustment for gender, age, pTNM stage, adjuvant therapies, and gastrectomy. The group with healthy weight (≥ 18.5 to $<23 \text{ kg}/m^2$) was the reference group. A two-sided p-value less than 0.05 was considered as statistically significant. All the statistical analyses were performed using SAS software v9.4 (SAS Institute, Inc., Cary, NC).

Results

Clinical characteristics

In this study, we defined 18 441 gastric cancer patients diagnosed between 1998–2018 (Table 1). Of these subjects, more than half of the patients were males (13 533, 73.4%) with a median age of 58.5 years. Among the total subjects, 84.5% experienced weight loss at diagnosis when compared with the usual weight, 40.5% had a smoking history, and 33.2% had a drinking history. During our follow-up, 4 717 (25.6%) deaths were recorded in our database.

Compared to healthy BMI at diagnosis, overweight and obese patients had more weight loss as 0 to 10% than patients with healthy weight (81.6% vs. 81.9% vs. 75.9%, $P < 0.001$). Underweight patients were more likely to be diagnosed at a later stage than other groups (pTNM IV, 17.0% vs. 13.7% vs. 10.6% vs. 9.6%, $P < 0.001$).

Current drinkers tended to be at later pTNM stage (stage IV, 44.2% vs. 12.6% vs. 11.9%, $P < 0.001$) and proximal location of stomach (47.0% vs. 33.4% vs. 34.5%) than never or former drinkers. In terms of cigarette smoking, former smokers were older (aged ≥ 66 years, 37.9% vs. 30.0% vs. 23.0%, $P < 0.001$) than never or current smokers. Current smokers are also more likely to be current alcohol drinkers (61.3% vs. 10.1% vs. 43.2%, $P < 0.001$) as compared to never or former smokers.

Survival outcomes in univariate analysis

Figure 2 showed the Kaplan-Meier curves for overall survival (OS) of different BMI at diagnosis with gastric cancer, no surgery, gastrectomy, and only curative gastrectomy patients. The median OS of total patients for each BMI category was as follows: underweight, 12.5 years; healthy weight, 13.0 years; overweight, 13.6 years; and obese, 13.6 years ($P < 0.001$). For no surgery patients, results are as follows: underweight, 5.7 years; healthy weight, 5.0 years; overweight, 5.9 years; and obese, 6.1 years ($P = 0.26$). For the gastrectomy group, survival status was as follows: underweight, 14.0 years; healthy weight, 14.0 years; overweight, 14.2 years; and obese, 14.4 years ($P < 0.001$). For the only curative gastrectomy, survival status was as follows: underweight, 14.1 years; healthy weight, 14.3 years; overweight, 14.3 years; and obese, 14.5 years ($P = 0.002$). The 3- and 5-year OS for different gastrectomy groups presented in Supplementary Table 1.

Kaplan-Meier survival comparisons (Supplementary Figure 1 and Supplementary Table 2) showed no association between smoking status and the overall survival of gastric cancer patients, even stratified in only the curative gastrectomy group. Concerning alcohol drinking, there was a significant difference between drinking status among no surgery patients ($P = 0.009$), but not in other groups (Supplementary Figure 2 and Supplementary Table 3). Survival of both smoking and alcohol drinking status was also analyzed (Figure 3 and Supplementary Table 4), significant differences were presented in total and gastrectomy groups.

Univariate analysis (Supplementary Table 5) showed that overweight and obese patients had a better survival than normal weights (HR = 0.92, 95% CI: 0.88–0.96, $P < 0.001$ and HR = 0.89, 95% CI: 0.83–0.96, $P = 0.001$, respectively), while the discrepancy of survival rates was attenuated in gastrectomy group (HR = 0.95, 95% CI: 0.90–1.00, $P = 0.04$ and HR = 0.91, 95% CI: 0.84–0.99, $P = 0.03$, respectively). For curative gastrectomy patients, however, only the overweight group showed an improved survival result (HR = 0.94, 95% CI: 0.89–1.00, $P = 0.049$). Weight loss as $>10\%$ of the usual weight was a significant risk factor of mortality for four groups ($P < 0.001$). As showed in Table 2, smoking history more than 30 years was a prognostic factor of poor survival

for total patients and gastrectomy patients ($P<0.001$). Drinking status, even heavy drinkers, however, was not a negative prognostic indicator.

Survival outcomes in multivariable analysis

J-shaped relationship between BMI at diagnosis and survival in patients in multivariate-adjusted of different gastrectomy groups revealed in Figure 4. The HR for total gastric cancer patients was the lowest (HR = 0.90; 95% CI: 0.86–0.94) at a BMI of 25.96, while BMI of 28.20 for no surgery patients, 25.47 for gastrectomy patients, 25.50 for only curative gastrectomy patients. Multivariable results (Table 2), however, indicated that BMI at diagnosis did not effect on prognosis.

For total gastric cancer patients, any weight loss ($P<0.001$), advanced pTNM stage ($P<0.001$), and gastrectomy status (HR = 1.51, 95% CI: 1.40–1.63, $P<0.001$) were independently associated with mortality. In surgery group, factors independently associated with poor survival include older age (≥ 66 years) (HR = 1.20, 95% CI: 1.05–1.38, $P = 0.001$), any weight loss (0 to 10%, HR = 1.13, 95% CI: 1.05–1.20, $P<0.001$ and $>10\%$, HR = 1.25, 95% CI: 1.14–1.38, $P<0.001$), smoking history more than 30 years (HR = 1.14, 95% CI: 1.04–1.24, $P = 0.004$), and advanced pTNM stage ($P<0.001$). An additional death-related factor for only curative gastrectomy group was meddle age (36–65 years) (HR = 1.15, 95% CI: 1.00–1.33, $P = 0.047$).

Discussion

This study investigated in a retrospective way how the lifestyle of gastric cancer patients was associated with prognosis, including BMI at diagnosis, smoking, and drinking. A primary finding of this study was that BMI at diagnosis was not independently associated with long-term survival after adjusting for other risk factors, although weight loss as both 0 to 10% and $>10\%$ of the usual weight was an adverse prognostic factor for gastric cancer patients.

We included 18 441 patients in this study, a larger cohort than most previous studies, and followed them for a prolonged period of more than ten years. Four particular subgroups, total patients, no surgery, gastrectomy, and only curative gastrectomy, were analyzed to eliminate the effect of gastrectomy which may affect the survival outcomes. After controlling confounding variables, we found that weight loss as any percentage of usual weight was associated with increased risk of mortality in gastric cancer patients than those with no weight loss. Perhaps it was since that human adipose tissue may have the function of preserving nutrients and increased the chance to survive when human body suffered from stress, as confronted with anti-cancer treatment [6, 34, 35]. And weight loss may due to gastric cancer-induced dysphagia, odynophagia, anorexia or cancer cachexia, thus it has a negative effect on survival [36].

Weight management strategies for gastric cancer patients have been gaining a lot of attention, and the relationship between obesity and cancer prognosis was complex. Many previous retrospective studies have also evaluated the association of BMI with the prognosis of gastric cancer in the general population; most of these studies, however, just analyzed the patients with gastrectomy. A recent study [6] from Korea, which covered a cohort of 7765 patients in a single institution, denoted that patients who were overweight or mild-to-moderately obese (BMI 23 to <30 kg/m²) preoperatively had better OS than those with healthy weights. Such a

result was similar to those of another study carried out in Japan, which included 7925 patients [20]. The reasons for the above outcomes may be as follow: primarily, it is more likely that obese patients who have suffered gastric cancer have less aggressive tumors [37, 38], which was consistent with the features in our study, i.e. the occurrence of pTNM IV tumors was more common in underweight patients. Furthermore, patients who were overweight or obese could get ideal BMI after gastrectomy, thus acquiring better long-term prognosis [38]. Also, a prospective study [39] with 1033 patients showed that it was just among the patients of 60 and older that lower BMI was associated with all-cause death, displaying a J-shaped pattern (HR = 2.28 for BMI <18.5; HR = 1.61 for 25 vs. 23.0 to <25.0 kg/m²). Conversely, higher BMI was also reported to promote the peritoneal dissemination of gastric cancer and had a worse survival rate in the study [40]. In summary, the clinical analysis mainly concluded that obesity was associated with improved survival of patients with gastric cancer. McQuade, J. L. et al. even indicated that high BMI cancer patients got improved response and survival with cancer treated with targeted therapy and checkpoint blockade immunotherapy, although a mechanistic link was not elucidated [41, 42].

Researches targeting the tumor microenvironment also investigated the impact of obesity on immune responses during cancer progression and therapy [43–45]. Trevellin E et al. reported that esophageal peritumoral adipose tissue and its secretion of tumor-promoting factors are directly correlated with increased tumor growth [46]. One study collected periprostatic and subcutaneous adipose tissue in culture with prostate cancer cells concluded that periprostatic adipose tissue among obese individuals providing a favorable environment for prostate cancer progression [47]. Adipocytes undergoing lipolysis was recognized as a source of lipids for cancer cells [48]. Furthermore, a recent study published in *Nature Medicine* demonstrate that obesity (BMI ≥ 30 kg/m²) results in increased immune aging, tumor progression and PD-1-mediated T cell dysfunction across multiple species and tumor models [45]. However, in our clinical study, BMI at diagnosis was not independently associated with long-term survival after multivariable analyses, even stratified in the gastrectomy group. More investigations are needed to clarify this issue in future studies because of the paradoxical effects of obesity between clinical and basic researches.

Shreds of evidence for the prognostic effect of drinking have been inconsistent. A meta-analysis of 6856 cases from 7 countries presented that drinkers had a lower survival rate, although there was significant heterogeneity between the included seven studies [49]. Our study revealed no significant association of drinking status and long-term prognosis, even in the subgroup for heavy drinkers (≥ 53.5 g/d). We guess that the differences may be partly attributed to the genetic distinction of populations with different race or regions.

Meanwhile, it was found that cigarette smoking was related to gastric cancer risk [23, 24, 50], and it also may have effects on affect prognosis. As has been demonstrated in most studies, smoking has a null or inverse influence on the overall survival status [26, 27, 30, 51]. It had been reported by Yuko et al. [25] from Japan a positive association for starting smoking at an earlier age. A possible explanation was that smoking increases serum estrogen metabolites, which have been postulated to induce a more aggressive tumor at a younger age. Moreover, it has been reported in two published studies [25, 32] that the risk of death caused by cancer increases if the patients undergoing curative gastrectomy have a smoking history. That was comparable with our research. In our multivariable outcome, we found that smoking history of more than 30 years conferred a worse prognosis in both gastrectomy and only curative gastrectomy groups. It may indicate that long-term cigarette smoking shows a significant effect on the risk of mortality for patients who underwent gastrectomy.

Although the cause of this association is unclear, possibilities can be considered. Smoking cigarette has an adverse effect on the pulmonary, circulatory, and immunologic systems, and on wound healing [33, 52]. The cumulative chronic toxic effects of long-term smoking may delay the recovery of gastrectomy patients with bad body condition and cause poor survival outcomes.

Several limitations need to be considered in this study. First, we do not have data on changes in lifestyle factors during treatment, or in the post-treatment phase. These measures collected systematically would allow for a better understanding of whether change following diagnosis is associated with cancer prognosis. Second, BMI has been used as the most common measure of indicating obesity due to its simplicity of measurement and availability. Waist circumference and actual body composition, particularly fat and muscle percentages, however, may be more reflective of the degree of someone's obesity. Thirdly, it just conducted in the single institution of China National Cancer Center, so the results might not be used as a reference for the whole Chinese population. However, it might have the reference value as the number of gastric cancer patients was large, and the patients usually came from Northern and Eastern areas in China. Another strength of this study was that the particular groups were analyzed included total patients, no surgery, gastrectomy and curative gastrectomy groups.

Conclusions

In conclusion, our results contribute to a better understanding of the role of lifestyles on the overall burden of gastric cancer with long-term prognosis. Among the total patients, weight loss (both 0 to 10% and >10% groups) but not BMI at diagnosis was related to survival results. For other factors, smoking history of more than 30 years conferred a worse prognosis for only gastrectomy patients. Extensive efforts are needed to elucidate mechanisms targeting the complex effects of lifestyles factors.

List Of Abbreviations

BMI, body mass index; NCCGCDB, China National Cancer Center Gastric Cancer Database; HRs, Hazard ratios; CIs, Confidence intervals; OS; overall survival.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee.

Approval Letter of Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College:

Institution name: National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Approval number:17–156/1412.

Consent for publication

Consent was obtained from all authors.

Availability of data and materials

All data generated or analysed during this study are included in this published article, included the supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Concept -LZ; Design - HH; Supervision - TW; Resources - HZ, Fuhai Ma; Materials - HR; Data Collection and/or Processing - CW; Analysis and/or Interpretation - XZ; Literature Search - CS, RL; Writing Manuscript - LZ; Critical Review - YC, DZ. All authors read and approved the final manuscript.

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Tables

Table 1. Comparisons of 18 441 gastric cancer patients' characteristics.

Characteristics, n (%)	No. of Patients	BMI at diagnosis				P	Drinkers			P	Smokers			P
		<18.5	18.5-22.9	23-27.4	≥27.5		Never	YES			Never	YES		
								Ex-drinkers	Current-drinkers			Ex-smokers	Current-smokers	
No. of patients	18,441 (100)	1,193 (6.5)	6,872 (37.3)	7,310 (39.6)	2,196 (11.9)	—	11,578 (62.8)	922 (5.0)	5,202 (28.2)	—	10,244 (55.6)	2,315 (12.6)	5,156 (28.0)	—
Gender														
Male	13,533 (73.4)	758 (63.5)	4,893 (71.2)	5,682 (77.7)	1,667 (75.9)		6,992 (62.0)	874 (95.8)	4,948 (96.6)		5,903 (57.6)	2,220 (95.5)	4,974 (96.5)	
Female	4,819 (26.1)	435 (36.5)	1,979 (28.8)	1,628 (22.3)	529 (24.1)	<0.001	4,286 (28.0)	38 (4.2)	174 (3.4)	<0.001	4,341 (42.4)	95 (4.1)	182 (3.5)	<0.001
Age at diagnosis (years)														
Mean (SD)	58.5	56.7	58.2	59.0	58.5	<0.001	58.6	60.1	58.2	<0.001	58.0	62.1	58.1	<0.001
Younger (≤35)	653 (3.5)	127 (10.7)	289 (4.2)	152 (2.1)	61 (2.8)		530 (4.6)	13 (1.4)	91 (1.8)		520 (5.1)	22 (1.0)	93 (1.8)	
Middle-aged (36-65)	12,119 (65.7)	682 (57.2)	4,604 (67.0)	5,063 (69.3)	1,524 (69.4)		7,373 (63.7)	657 (71.3)	3,887 (74.7)		6,640 (64.8)	1,415 (61.1)	3,872 (75.1)	
Older (≥66)	5,235 (28.4)	383 (32.1)	1,976 (28.8)	2,090 (28.6)	609 (27.7)	<0.001	3,667 (31.7)	252 (27.3)	1,220 (23.5)	<0.001	3,077 (30.0)	877 (37.9)	1,188 (23.0)	<0.001
Weight loss as % of usual weight														
None	2,858 (15.5)	164 (13.8)	821 (12.0)	813 (11.1)	276 (12.6)		1,629 (14.1)	53 (5.8)	642 (12.3)		1,437 (14.0)	261 (11.3)	625 (12.1)	
0-10	13,814 (74.9)	766 (64.2)	5,217 (75.9)	5,964 (81.6)	1,798 (81.9)		8,830 (76.3)	766 (83.1)	4,030 (77.5)		7,825 (76.4)	1,835 (79.3)	3,980 (77.2)	
≥10	1,769 (9.6)	263 (22.1)	834 (12.1)	533 (7.3)	122 (5.6)	<0.001	1,119 (9.7)	103 (11.2)	530 (10.2)	<0.001	982 (9.6)	219 (9.5)	551 (10.7)	0.0001
Smoking status														
Never smokers	10,244 (55.6)	737 (61.8)	3,895 (56.7)	4,084 (55.9)	1,252 (57.0)		9,081 (78.4)	124 (13.5)	1,037 (19.9)		—	—	—	
Smokers	7,471 (40.5)	435 (36.5)	2,875 (41.8)	3,128 (42.8)	922 (42.0)	0.002	2,488 (21.5)	795 (86.2)	4,159 (80.0)	<0.001	—	—	—	—
Current smokers	5,156 (28.0)	339 (28.4)	2,076 (30.2)	2,059 (28.2)	604 (27.5)		1,733 (15.0)	250 (27.1)	3,158 (60.7)		—	—	—	
Ex-smokers	2,315 (12.6)	96 (8.1)	799 (11.6)	1,069 (14.6)	318 (14.5)	<0.001	755 (6.5)	545 (59.1)	1,001 (19.2)	<0.001	—	—	—	—
Time since quitting smoking														
Short-term (1-9 years)	1,505 (8.2)	75 (6.3)	535 (7.8)	678 (9.3)	197 (9.0)		474 (4.1)	422 (45.8)	597 (11.5)		0 (0.0)	1,505 (65.0)	0 (0.0)	
Long-term (≥10 years)	810 (4.4)	21 (1.8)	264 (3.8)	391 (5.4)	121 (5.5)	<0.001	281 (2.4)	123 (13.3)	404 (7.8)	<0.001	0 (0.0)	810 (35.0)	0 (0.0)	<0.001
No. of cigarettes (per day)														
≤20 (1 pack)	5,568 (30.2)	338 (28.3)	2,190 (31.9)	2,318 (31.7)	642 (29.2)		1,919 (16.6)	602 (65.3)	3,030 (58.3)		0 (0.0)	1,770 (76.5)	3,798 (73.7)	
21-39	457 (2.5)	22 (1.8)	164 (2.4)	198 (2.7)	62 (2.8)		144 (1.2)	36 (3.9)	276 (5.3)		0 (0.0)	115 (5.0)	342 (6.6)	
≥40 (≥2 packs)	708 (3.8)	32 (2.7)	250 (3.6)	302 (4.1)	113 (5.2)	<0.001	228 (2.0)	76 (8.2)	400 (7.7)	<0.001	0 (0.0)	208 (9.0)	500 (9.7)	<0.001
Duration of smoking (years)														
1-29	2,805 (15.2)	131 (11.0)	999 (14.5)	1,258 (17.2)	383 (17.4)		927 (8.0)	372 (40.4)	1,497 (28.8)		0 (0.0)	1,230 (53.1)	1,575 (30.6)	
≥30	4,037 (21.9)	267 (22.4)	1,652 (24.0)	1,604 (21.9)	449 (20.5)	<0.001	1,411 (12.2)	359 (38.9)	2,252 (43.3)	<0.001	0 (0.0)	940 (40.6)	3,097 (60.1)	<0.001
Alcohol consumption														

Never drinkers	11,578 (62.8)	862 (72.3)	4,520 (65.8)	4,549 (62.2)	1,347 (61.3)	—	—	—	—	9,081 (88.7)	755 (32.6)	1,733 (33.6)	
Drinkers	6,124 (33.2)	311 (26.1)	2,247 (32.7)	2,655 (36.3)	821 (37.4)	<0.001	—	—	—	1,161 (11.3)	1,546 (66.8)	3,408 (66.1)	<0.001
Current drinkers	5,202 (28.2)	272 (22.8)	1,909 (27.8)	2,249 (30.8)	692 (31.5)		—	—	—	1,037 (10.1)	1,001 (43.2)	3,158 (61.3)	
Ex-drinkers	922 (5.0)	39 (3.3)	338 (4.9)	406 (5.6)	129 (5.9)	<0.001	—	—	—	124 (1.2)	545 (23.5)	250 (4.9)	<0.001

Amount of alcohol consumption

Light drinkers (<15.6 g/d)	102 (0.6)	3 (0.3)	40 (0.6)	48 (0.7)	11 (0.5)		0 (0.0)	15 (1.6)	87 (1.7)		15 (0.2)	42 (1.8)	45 (0.9)
Moderate drinkers (≥ 15.6 g/d to <53.5 g/d)	660 (3.6)	30 (2.5)	246 (3.6)	311 (4.3)	62 (2.8)		0 (0.0)	77 (8.4)	583 (11.2)		127 (1.2)	201 (8.7)	329 (6.4)
Heavy drinkers (≥ 53.5 g/d)	3,480 (18.9)	167 (14.0)	1,277 (18.6)	1,488 (20.4)	501 (22.8)	<0.001	0 (0.0)	593 (64.3)	2,887 (55.5)	<0.001	620 (6.1)	894 (38.6)	1,962 (38.1)

H. pylori

No	1,506 (8.2)	67 (5.6)	561 (8.2)	668 (9.1)	193 (8.8)		837 (7.2)	152 (16.5)	489 (9.4)		734 (7.2)	272 (11.8)	474 (9.2)
Yes	1,167 (6.3)	56 (4.7)	457 (6.7)	503 (6.9)	134 (6.1)	<0.001	692 (6.0)	74 (8.0)	386 (7.4)	<0.001	590 (5.8)	169 (7.3)	393 (7.6)

Histologic type

Well	351 (1.9)	27 (2.3)	107 (1.6)	165 (2.3)	48 (2.2)		214 (1.9)	24 (2.6)	107 (2.1)		185 (1.8)	45 (1.9)	115 (2.2)
Moderately	5,514 (29.9)	257 (21.5)	2,004 (29.2)	2,390 (32.7)	758 (34.5)		2,300 (28.5)	288 (31.2)	1,829 (36.2)		2,789 (27.2)	844 (36.5)	1,787 (34.7)
Poorly	5,824 (31.6)	374 (31.4)	2,236 (32.5)	2,398 (32.8)	730 (33.2)		3,922 (33.9)	233 (25.3)	1,567 (30.1)		3,643 (35.6)	612 (26.4)	1,475 (28.6)
Undifferentiated, anaplastic	3 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)	0 (0.0)	<0.001	1 (0.0)	0 (0.0)	2 (0.0)	<0.001	3 (0.0)	0 (0.0)	0 (0.0)

pathologicT

p0	61 (0.3)	2 (0.2)	22 (0.3)	27 (0.4)	10 (0.5)		41 (0.4)	3 (0.3)	17 (0.3)		35 (0.3)	7 (0.3)	19 (0.4)
p1	2,778 (15.1)	131 (11.0)	966 (14.1)	1,242 (17.0)	412 (18.8)		1,810 (15.6)	206 (22.3)	721 (13.9)		1,663 (16.2)	347 (15.0)	729 (14.1)
p2	1,524 (8.3)	83 (7.0)	528 (7.7)	647 (8.9)	243 (11.1)		955 (8.3)	75 (8.1)	462 (8.9)		834 (8.1)	192 (8.3)	467 (9.1)
p3	3,340 (18.1)	169 (14.2)	1,233 (17.9)	1,459 (20.0)	443 (20.2)		2,051 (17.7)	176 (19.1)	1,093 (21.0)		1,702 (16.6)	497 (21.5)	1,120 (21.7)
p4	6,545 (35.5)	465 (39.0)	2,605 (37.9)	2,640 (36.1)	708 (32.2)	<0.001	4,308 (37.2)	266 (28.9)	1,882 (36.2)	<0.001	3,888 (38.0)	812 (35.1)	1,765 (34.2)

pathologicN

p0	4,964 (26.9)	274 (23.0)	1,758 (25.6)	2,184 (29.9)	685 (31.2)		3,149 (27.2)	304 (33.0)	1,436 (27.6)		2,785 (27.2)	670 (28.9)	1,434 (27.8)
p1	2,426 (13.2)	161 (13.5)	905 (13.2)	1,008 (13.8)	313 (14.3)		1,577 (13.6)	116 (12.6)	709 (13.6)		1,357 (13.3)	301 (13.0)	744 (14.4)
p2	2,549 (13.8)	170 (14.3)	1,018 (14.8)	997 (13.6)	327 (14.9)		1,639 (14.2)	116 (12.6)	758 (14.6)		1,448 (14.1)	316 (13.7)	753 (14.6)
p3	4,045 (21.9)	226 (18.9)	1,570 (22.9)	1,717 (23.5)	464 (21.1)	<0.001	2,633 (22.7)	175 (19.0)	1,193 (22.9)	0.007	2,384 (23.3)	545 (23.5)	1,079 (20.9)

pathologicM

p0	14,785 (80.2)	899 (75.4)	5,563 (81.0)	6,176 (84.5)	1,889 (86.0)		9,438 (81.5)	770 (83.5)	4,373 (84.1)		8,348 (81.5)	1,971 (85.1)	4,273 (82.9)
p1	2,233 (12.1)	203 (17.0)	943 (13.7)	776 (10.6)	211 (9.6)	<0.001	1,460 (12.6)	110 (11.9)	620 (11.9)	<0.001	1,332 (13.0)	231 (10.0)	628 (12.2)

pTNM

I	3,340	157	1,155	1,490	500		2,139	221	16 (0.3)		1,928	435	922
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	(18.1)	(13.2)	(16.8)	(20.4)	(22.8)		(18.5)	(24.0)			(18.8)	(18.8)	(17.9)
II	2,334	137	843	1,012	320		1,443	147	922		1,210	317	782
	(12.7)	(11.5)	(12.3)	(13.8)	(14.6)		(12.5)	(15.9)	(17.7)		(11.8)	(13.7)	(15.2)
III	7,712	481	3,005	3,180	917		5,009	312	724		4,456	1,012	2,165
	(41.8)	(40.3)	(43.7)	(43.5)	(41.8)		(43.3)	(33.8)	(13.9)		(43.5)	(43.7)	(42.0)
IV	2,233	203	943	776	211	<0.001	1,460	110	2,301	<0.001	1,332	231	628
	(12.1)	(17.0)	(13.7)	(10.6)	(9.6)		(12.6)	(11.9)	(44.2)		(13.0)	(10.0)	(12.2)
Lauren classification													
Intestinal	2,838	126	988	1,304	388		1,549	250	995		1,279	554	962
	(15.4)	(10.6)	(14.4)	(17.8)	(17.7)		(13.4)	(27.1)	(19.1)		(12.5)	(23.9)	(18.7)
Diffuse	2,610	154	1,017	1,095	318		1,660	181	726		1,547	342	680
	(14.2)	(12.9)	(14.8)	(15.0)	(14.5)		(14.3)	(19.6)	(14.0)		(15.1)	(14.8)	(13.2)
Mixed	1,799	68	646	795	271	<0.001	1,010	146	621	<0.001	897	295	583
	(9.8)	(5.7)	(9.4)	(10.9)	(12.3)		(8.7)	(15.8)	(11.9)		(8.8)	(12.7)	(11.3)
Linitis plastica													
No	17,321	1,132	6,611	7,059	2,115		11,149	892	5,011		9,844	2,244	4,978
	(93.9)	(94.9)	(96.2)	(96.6)	(96.3)		(96.3)	(96.8)	(96.3)		(96.1)	(96.9)	(96.6)
Yes	181	23	80	59	16	0.005	125	9	44	0.55	117	18	43
	(1.0)	(1.9)	(1.2)	(0.8)	(0.7)		(1.1)	(1.0)	(0.9)		(1.1)	(0.8)	(0.8)
location													
Proximal GC	6,704	386	2,409	2,856	913		3,870	318	2,447		3,147	1,193	2,298
	(36.4)	(32.4)	(35.1)	(39.1)	(41.6)		(33.4)	(34.5)	(47.0)		(30.7)	(51.5)	(44.6)
Distal GC	9,992	704	3,966	3,948	1,141		6,884	517	2,417		6,354	933	2,545
	(54.2)	(59.0)	(57.7)	(54.0)	(52.0)		(59.5)	(56.1)	(46.5)		(62.0)	(40.3)	(49.4)
Total GC	894	56	353	355	104	<0.001	558	55	263	<0.001	507	127	240
	(4.9)	(4.7)	(5.1)	(4.9)	(4.7)		(4.8)	(6.0)	(5.1)		(5.0)	(5.5)	(4.7)
Type of gastrectomy													
Gastrectomy	15,204	930	5,623	6,248	1,885		9,662	773	4,278		8,533	1,961	4,230
	(82.5)	(78.0)	(81.8)	(85.5)	(85.8)		(83.5)	(83.8)	(82.2)		(83.3)	(84.7)	(82.0)
No surgery	3,146	263	1,246	1,061	311	<0.001	1,916	148	924	0.019	1,711	353	926
	(17.1)	(22.1)	(18.1)	(14.5)	(14.2)		(16.6)	(16.1)	(17.8)		(16.7)	(15.3)	(18.0)
Surgical Margin													
Negative	13,370	791	5,012	5,650	1,730		8,623	684	3,899		7,622	1,755	3,841
	(72.5)	(66.3)	(72.9)	(77.3)	(78.8)		(74.5)	(74.2)	(75.0)		(74.4)	(75.8)	(74.5)
Positive	443	36	163	195	41	<0.001	297	21	120	0.83	263	67	108
	(2.4)	(3.0)	(2.4)	(2.7)	(1.9)		(2.6)	(2.3)	(2.3)		(2.6)	(2.9)	(2.1)
Assitant therapy													
No neo/adjuvant	1,564	82	520	701	241		925	128	484		840	242	456
	(8.5)	(6.9)	(7.6)	(9.6)	(11.0)		(8.0)	(13.9)	(9.3)		(8.2)	(10.5)	(8.8)
Neoadjuvant	354	25	158	134	33		192	43	113		171	81	97
	(1.9)	(2.1)	(2.3)	(1.8)	(1.5)		(1.7)	(4.7)	(2.2)		(1.7)	(3.5)	(1.9)
Adjuvant	4,713	244	1,743	2,044	621		3,057	198	1,383		2,782	503	1,354
	(25.6)	(20.5)	(25.4)	(28.0)	(28.3)		(26.4)	(21.5)	(26.6)		(27.2)	(21.7)	(26.3)
Neo + adjuvant	613	37	222	272	77	<0.001	353	63	190	<0.001	319	136	154
	(3.3)	(3.1)	(3.2)	(3.7)	(3.5)		(3.1)	(6.8)	(3.7)		(3.1)	(5.9)	(3.0)

Table 2. Multivariate survival analysis.

Prognostic Factors	Total (n=18,322) ¹				No surgery (n=3,142) ²				Gastrectomy (n=15,180) ³				Only curative gastrectomy (n=13,695) ⁴			
	HR	95% CI		P Value	HR	95% CI		P Value	HR	95% CI		P Value	HR	95% CI		P Value
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Gender																
Male	1.00				1.00				1.00				1.00			
Female	1.05	1.00	1.11	0.06	1.07	0.97	1.19	0.19	1.05	0.99	1.11	0.13	1.04	0.97	1.11	0.25
Age at diagnosis (years)																
Younger (≤35)	1.00				1.00				1.00				1.00			
Middle-aged (36-65)	1.07	0.95	1.19	0.26	0.94	0.76	1.15	0.54	1.14	0.99	1.30	0.06	1.15	1.00	1.33	0.05
Older (≥66)	1.10	0.98	1.23	0.12	0.89	0.72	1.11	0.30	1.20	1.05	1.38	0.01	1.21	1.05	1.40	0.01
BMI (kg/m ²) at diagnosis																
<18.5	1.00	0.92	1.09	0.99	1.01	0.87	1.18	0.90	1.00	0.90	1.10	0.93	1.02	0.92	1.14	0.72
18.5-22.9	1.00				1.00				1.00				1.00			
23-27.4	0.97	0.93	1.02	0.22	0.92	0.84	1.02	0.11	0.99	0.94	1.05	0.73	0.99	0.94	1.05	0.74
≥27.5	0.99	0.92	1.06	0.72	0.95	0.82	1.10	0.48	1.01	0.93	1.10	0.85	1.02	0.93	1.11	0.74
Weight loss as % of usual weight																
None	1.00				1.00				1.00				1.00			
0-10	1.14	1.07	1.20	<0.001	1.16	1.04	1.30	0.01	1.13	1.05	1.20	0	1.11	1.04	1.19	0
≥10	1.24	1.15	1.34	<0.001	1.22	1.06	1.40	0.01	1.25	1.14	1.38	<0.001	1.22	1.10	1.34	0
Smoking status																
Never smokers	1.00				1.00				1.00				1.00			
Current smokers	1.02	0.94	1.10	0.66	1.05	0.89	1.23	0.57	1.01	0.92	1.11	0.78	1.03	0.93	1.14	0.58
Ex-smokers	0.93	0.84	1.03	0.17	0.95	0.76	1.19	0.66	0.93	0.82	1.04	0.20	0.91	0.81	1.03	0.15
Time since quitting smoking																
Short-term (1-9 years)	1.00				1.00				1.00				1.00			
Long-term (≥10 years)	1.04	0.91	1.19	0.55	1.02	0.78	1.34	0.87	1.05	0.90	1.22	0.51	1.07	0.91	1.25	0.42
No. of cigarettes (per day)																
≤20 (1 pack)	1.00				1.00				1.00				1.00			
21-39	1.07	0.93	1.22	0.36	1.29	1.00	1.66	0.05	0.98	0.84	1.16	0.84	0.99	0.83	1.17	0.87
≥40 (≥2 packs)	1.03	0.92	1.16	0.59	0.91	0.72	1.15	0.43	1.09	0.95	1.24	0.22	1.08	0.94	1.24	0.30
Duration of smoking (years)																
1-29	1.00				1.00				1.00				1.00			
≥30	1.08	1.00	1.16	0.05	0.94	0.81	1.09	0.40	1.14	1.04	1.24	0	1.13	1.04	1.24	0.01
Alcohol consumption																
Never drinkers	1.00				1.00				1.00				1.00			
Current drinkers	0.82	0.58	1.18	0.29	1.54	0.71	3.37	0.28	0.75	0.50	1.12	0.16	0.88	0.59	1.32	0.54
Ex-drinkers	0.86	0.59	1.24	0.42	1.33	0.63	2.80	0.46	0.75	0.49	1.16	0.19	0.86	0.56	1.32	0.48
Amount of alcohol consumption																
Light drinkers (<15.6 g/d)	1.00				1.00				1.00				1.00			
Moderate drinkers (≥15.6 g/d to <53.5 g/d)	1.25	0.86	1.81	0.25	0.97	0.45	2.13	0.95	1.27	0.83	1.94	0.28	1.07	0.70	1.64	0.75
Heavy drinkers (≥53.5 g/d)	1.25	0.88	1.79	0.21	0.78	0.37	1.66	0.52	1.37	0.91	2.06	0.13	1.15	0.77	1.73	0.50
pTNM																
I	1.00				1.00				1.00				1.00			

II	1.48	1.33	1.66	<0.001	3.65	0.45	29.50	0.23	1.48	1.32	1.65	<0.001	1.38	1.23	1.56	<0.001
III	2.31	2.12	2.52	<0.001	4.07	0.56	29.79	0.17	2.29	2.10	2.49	<0.001	2.19	2.00	2.39	<0.001
IV	3.19	2.86	3.55	<0.001	4.41	0.62	31.18	0.14	3.42	3.04	3.86	<0.001	3.16	2.79	3.58	<0.001
Type of gastrectomy																
Gastrectomy	1.00				—					—			—			
No surgery	1.51	1.40	1.63	<0.001	—	—	—	—	—	—	—	—	—	—	—	—

¹Adjust for gender, age, pTNM stage, adjuvant therapies, gastrectomy.

²Adjust for gender, age, pTNM stage.

³Adjust for gender, age, pTNM stage, adjuvant therapies.

⁴Adjust for gender, age, pTNM stage, adjuvant therapies.

Figures

Figure 1

The geographical locations of gastric cancer patients of NCCGCDB, 1999–2018. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 2

Kaplan-Meier survival curves for overall survival of different BMI at diagnosis. A. Total gastric cancer patients. B. No surgery patients. C. Gastrectomy patients. D. Only curative gastrectomy patients.

Figure 3

Kaplan-Meier survival curves for overall survival of both smoking and drinking status. A. Total gastric cancer patients. B. No surgery patients. C. Gastrectomy patients. D. Only curative gastrectomy patients.

Figure 4

BMI at diagnosis and overall survival in Multivariate-adjusted. A. Total gastric cancer patients. B. No surgery patients. C. Gastectomy patients. D. Only curative gastrectomy patients.

Supplementary Files

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