Prognostic Impact of Body Mass Index Stratified by Smoking Status in Patients With Esophageal Adenocarcinoma

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ABSTRACT

Purpose

Given that smoking affects body mass index (BMI) and survival, stratification by smoking status may be required to determine the true prognostic impact of BMI. Although obesity increases risk for developing esophageal adenocarcinoma (EAC), the prognostic influence of obesity and its potential modification by smoking status is unknown in this disease.

Patients and Methods

All patients (N = 778) underwent potentially curative esophagectomy. BMI was calculated using measured height and weight at surgery and categorized as obese (≥ 30 kg/m²), overweight (25 to 29.9 kg/m²), or normal (18.5 to 24.9 kg/m²). Cigarette smoking was categorized as never or ever. The association of BMI with disease-specific survival (DSS), disease-free survival (DFS), and overall survival (OS) was determined by Cox regression.

Results

Excess BMI was significantly associated with DSS in a manner that differed substantially by smoking status (*P* for interaction = .023). Among never smokers, obesity was significantly associated with adverse DSS (hazard ratio [HR] = 2.11; 95% CI, 1.31 to 3.43; *P* = .002), DFS (HR = 2.03; 95% CI, 1.30 to 3.18; *P* = .002), and OS (HR = 1.97; 95% CI, 1.24 to 3.14; *P* = .004), as compared with normal weight, after adjusting for covariates. By contrast, among ever smokers, obesity was not prognostic, and overweight status was significantly associated with favorable survival in univariate, but not multivariate, analysis.

Conclusion

Obesity among never smokers was independently associated with two-fold worsening of DSS, DFS, and OS after surgery for EAC, after adjusting for known prognostic factors. These data, in one of the largest reported resected EAC cohorts, are the first to show an adverse prognostic impact of obesity in EAC.

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INTRODUCTION

The incidence of esophageal adenocarcinoma, including tumors of the gastroesophageal junction (GEJ) and gastric cardia (collectively referred to as esophageal adenocarcinoma [EAC]¹⁻³), is one of the fastest rising in the United States, paralleling the increase in obesity.⁴ Despite the use of aggressive therapy consisting primarily of surgical resection, EAC remains highly fatal.⁵ Among US males, esophageal cancer had the highest death rate among malignancies with increasing mortality trends from 1990 to 2006 and ranks as the fifth leading cause of cancer death in ages 40 to 79 years.⁶ Although a higher body mass index (BMI) increases the risk of developing EAC, it is unknown whether obesity affects survival in patients with EAC.⁷⁻¹⁰ Such information could inform patient prognosis and

facilitate the development of novel therapeutic strategies. Under the hypotheses that hyperinsulinemia and other metabolic derangements linked to adiposity may promote tumor growth and progression, obesity has been associated with adverse outcome in other cancers, including the pancreas and colon.¹¹⁻¹⁶ Yet, studies in patients with EAC have reported that excess BMI has a null, or even protective, effect on prognosis.

Examination of BMI and survival has increasingly drawn attention to the importance of accounting for cigarette smoking status. Smoking is known to affect BMI and all-cause mortality and has also been shown to attenuate the increase in relative mortality due to excess BMI, with multiple population-based cohort studies showing stronger associations between obesity and mortality in never, as compared with ever, smokers.¹⁷⁻²⁰ Accordingly,

the true prognostic impact of BMI may be understood only after stratifying by smoking status or excluding smokers.¹⁷⁻²⁰ The effect of smoking in modulating the association between BMI and mortality may be more pronounced in smoking-related cancers such as EAC, because smoking has been associated with higher risk of developing EAC²¹ and is common in patients with EAC.²²⁻²⁴

The study of BMI and outcome in EAC has been impeded by several factors. EAC has been conflated with subcardial gastric cancers or esophageal squamous cell carcinomas, both of which are epidemiologically and clinically distinct from EAC.^{1,2,25} Among patients from the same study, body weight has been ascertained at variable times relative to diagnosis or therapy, or has been estimated, rather than measured. Studies have generally been small in size and number and have infrequently accounted for smoking status.^{20,23,24,26,27} In addition, EAC study populations have received a diverse set of therapies, commonly including preoperative chemotherapy and/or radiation, which can profoundly affect nutritional intake and BMI.²⁸

To address these questions, we analyzed BMI while stratifying by smoking status in a large cohort of patients with EAC that was homogeneous by histology and limited to the esophagus, GEJ, or gastric cardia. Height and weight were measured at uniform time points relative to diagnosis and surgery. In addition, we limited the cohort to patients who underwent surgical resection before 1998, before perioperative chemotherapy and/or radiotherapy were routinely used for resectable disease at our institution and other US medical centers.²⁹

PATIENTS AND METHODS

Study Cohort

Our study cohort originates from the Mayo Esophageal Cancer Outcomes Database, which has been previously described.³⁰ Briefly, this cohort consists of all adult patients with newly diagnosed, pathologically confirmed adenocarcinoma of the esophagus, GEJ, or gastric cardia who underwent surgical resection with cancer-free margins at Mayo Clinic in Rochester, MN (January 1, 1980, to December 31, 1997). Subcardial gastric cancers and tumors with only nonadenocarcinoma histology were excluded. The database was developed using clinical information systematically extracted from medical records by trained physicians using a standardized abstraction form. Independent data review was performed for quality assurance, and all data entry was checked for accuracy by administrative research staff. A total of 796 patients met all inclusion criteria and comprised the parent study cohort.

Collection of BMI and Smoking Data

Height and weight was measured at Mayo on all patients at the time of esophagectomy. Data on cigarette smoking and weight loss in the year before surgery were prospectively collected by clinical staff on patients undergoing esophagectomy at Mayo. Within 2 weeks before their surgery, patients completed a written institutional questionnaire asking specifically about current³¹ and past cigarette use and changes in weight. Each patient's responses were verified on the date of questionnaire completion during a visit with their Mayo primary care physician.

Of 796 patients in the parent cohort, nine patients received neoadjuvant chemo- and/or radiotherapy and were excluded. Of remaining patients, nine were underweight (BMI < 18.5 kg/m²) and were excluded. Therefore, 778 patients comprise the current study population.

Clinical End Points and Statistical Analysis

Our primary clinical outcome variable was disease-specific survival (DSS), defined as the time from surgery to death related to EAC, censored at the date of death resulting from postoperative complications or other nonmalignant causes. Secondary end points included disease-free survival (DFS) and overall survival (OS). OS was defined as the time from surgery

to death resulting from any cause and DFS as the time from surgery to the first recurrence of index cancer or to all-cause death. Death beyond 5 years was censored.

World Health Organization cut points were used to categorize patients by BMI as very obese (≥ 35 kg/m²), obese (≥ 30.0 to 34.9 kg/m²), overweight (≥ 25.0 to 29.9 kg/m²), and normal weight (≥ 18.5 to 24.9 kg/m²).³² Given the small number of very obese patients, very obese and obese groups were analyzed in combination. Kaplan-Meier and Cox proportional hazards models were used to assess the association between predictor variables and outcomes. Wilcoxon rank sum and χ^2 tests were used to compare continuous and categorical variables between groups, respectively. To assess whether the effect of BMI on DSS was modified by smoking status, an interaction term (ie, the product of categorical BMI and smoking status [ever v never]) was included in the Cox model in addition to BMI and smoking status. The primary multivariate Cox model included tumor stage and grade (American Joint Committee on Cancer criteria, 7th edition, 2009). Age, sex, and presurgery weight loss ($\geq 10\%$) were added in subsequent models³³⁻³⁵; given that results were highly stable, multivariate models containing all covariates are reported. For ever smokers, number of pack-years was also included as indicated. Hazard ratios (HRs) with 95% CIs and two-sided *P* values were reported. *P* $\leq .05$ was considered statistically significant. Analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC). Study data were collected using REDCap electronic data capture tools hosted at Mayo.³⁶ The study was approved by the Mayo institutional review board.

RESULTS

Overall Study Population

The study population (N = 778) is from the Mayo Esophageal Cancer Outcomes Database as described.³⁰ Baseline clinicopathologic characteristics are shown in Table 1. In brief, all patients had adenocarcinomas and underwent surgery at Mayo with cancer-free margins. Most patients were male (89%) and had locally advanced tumor stage (80% were IIB to IIIC). By anatomic site, 279 tumors (36%) were esophageal, 458 (59%) were GEJ, and 40 (5%) were limited to the gastric cardia. The nine patients who were underweight were excluded. No patient received neoadjuvant therapy, and 625 patients (80%) did not receive postoperative adjuvant therapy. Postoperative chemotherapy alone, radiotherapy alone, and concurrent chemoradiotherapy was delivered in 27 (3.5%), 23 (3.0%), and 53 (6.8%) patients, respectively; adjuvant therapy status was unknown in 50 patients (6.3%). Chemotherapy agents delivered in various combinations included fluorouracil (n = 67), doxorubicin (n = 27), cisplatin (n = 7), mitomycin (n = 5), carboplatin (n = 1), etoposide (n = 1), and not recorded or other (n = 7). Ivor-Lewis, transhiatal, and other surgeries were performed in 546 (70%), 112 (14%), and 120 (15%) patients, respectively. Median follow-up for assessment of vital status and disease recurrence was 12.9 and 5.0 years, respectively.

Smoking status, and measured height and weight at surgery, was available for all patients. Among never smokers (n = 236), 46 (19%) were obese, 117 (50%) were overweight, and 73 (31%) had normal weight. Among ever smokers (n = 542; median 37 pack-years [range, 1 to 280]), 125 (23%) were obese, 231 (43%) were overweight, and 186 (34%) had normal weight. Never (v ever) smoking status was associated with older age and female sex, consistent with prior literature^{37,38} (Table 1).

BMI, Smoking, and Survival

For DSS, the BMI $\times$ smoking interaction term was significant (*P* = .023), indicating that the prognostic impact of excess BMI

Table 1. Baseline Characteristics at Surgery by Smoking Status in Patients With Esophageal Adenocarcinoma

Characteristic	Overall (N = 778)		Never Smokers (n = 236)		Ever Smokers (n = 542)		P
	No.	%	No.	%	No.	%	
Sex							
Male	692	89	192	81	500	92	< .001
Female	86	11	44	19	42	8	
Age, years							< .001
Median	65		68		64		
Range	22-89		22-89		30-88		
Stage							.138
IIIC	127	17	38	16	89	17	
IIIB	173	23	56	24	117	22	
IIIA	160	21	40	17	120	23	
IIB	144	19	55	24	89	17	
IA to IIA	156	20	44	19	112	22	
Grade							.225
4	300	39	84	36	216	41	
1 to 3	467	61	150	64	317	59	
Weight loss in the year preceding surgery							.177
≥ 10%	174	22	60	25	114	21	
< 10%	604	78	176	75	428	79	
Body mass index							.192
Obese	171	22	46	19	125	23	
Overweight	348	45	117	50	231	43	
Normal	259	33	73	31	186	34	

differed significantly on the basis of smoking status. Among never smokers ($n = 236$), univariate analysis revealed that obese patients had significantly shorter DSS as compared with normal-weight patients ($HR = 1.62$; 95% CI, 1.03 to 2.53; $P = .034$; Fig 1). Overweight patients did not have significantly different DSS as compared with normal-weight patients. In this regard, among never smokers, only 18% of obese patients had not died as a result of EAC 5 years after surgery, as compared with 32% of overweight and 36% of normal weight patients (Tables 2 and 3). Other covariates were not associated with DSS (Table 2). For DFS, among never smokers, obesity was associated with worse DFS ($HR = 1.48$; 95% CI, 0.97 to 2.25), as

Fig 1. Disease-specific survival in never smokers after curative resection for esophageal adenocarcinoma according to body mass index at the time of surgery ($n = 236$). HR, hazard ratio.

compared with normal weight, though this association did not reach statistical significance ($P = .066$). Overweight status did not confer worse DFS as compared with normal weight. Univariate results were similar for OS (data not shown). In multivariable analysis among never smokers, obesity was significantly associated with adverse DSS ($HR = 2.11$; 95% CI, 1.31 to 3.43; $P = .002$), DFS ($HR = 2.03$; 95% CI, 1.30 to 3.18; $P = .002$), and OS ($HR = 1.97$; 95% CI, 1.24 to 3.14; $P = .004$), as compared with normal weight, after adjusting for tumor stage, grade, age, presurgical weight loss, and sex (Table 3, Fig 2). By contrast, overweight status was not significantly associated with adverse DSS, DFS, or OS, as compared with normal weight among never smokers (Table 3, Fig 2). Results were similar after adjustment for the presence of Barrett's esophagus and surgery type (data not shown).

In univariate analysis among ever smokers ($n = 542$), overweight status was significantly associated with longer DSS ($HR = 0.72$; 95% CI, 0.57 to 0.92; $P = .008$), DFS ($HR = 0.76$; 95% CI, 0.60 to 0.96; $P = .020$), and OS ($HR = 0.74$; 95% CI, 0.58 to 0.94; $P = .012$), as compared with normal weight. Obese patients did not have significantly different DSS, DFS, or OS as compared with normal-weight patients. In this regard, among ever smokers, 39% of overweight patients had not died as a result of EAC 5 years after surgery, as compared with 33% of obese and 28% of normal weight patients (Table 3). However, in multivariable analysis among ever smokers, the association of overweight status with DSS, DFS, and OS showed only marginal statistical significance. Among ever smokers, obesity was not associated with survival in multivariate analysis (Table 3, Fig 2). For all analyses among ever smokers, results were similar after adjustment for pack-years (data not shown).

Table 2. Disease-Specific Survival According to Clinicopathologic Variables in Univariate and Multivariate Analysis Among Never Smokers (n = 236)

Clinicopathologic Variable	Univariate			Multivariate*		
	HR	95% CI	P	HR	95% CI	P
Sex						
Male	1.57	1.00 to 2.47	.049	1.25	0.76 to 2.05	.370
Female	Ref			Ref		
Age, per year increase	1.00	0.99 to 1.02	.841	1.01	0.99 to 1.02	.378
Stage						
IIIC	14.16	6.73 to 29.81	< .0001	11.98	5.60 to 25.63	< .0001
IIIB	10.55	5.11 to 21.79	< .0001	11.19	5.32 to 23.54	< .0001
IIIA	7.96	3.81 to 16.64	< .0001	7.57	3.59 to 15.98	< .0001
IIB	3.96	1.80 to 8.30	.0003	4.12	1.96 to 8.66	.0002
IA to IIA	Ref			Ref		
Grade						
4	1.61	1.17 to 2.22	.0038	1.17	0.83 to 1.65	.374
1 to 3	Ref			Ref		
Weight loss in the year preceding surgery						
≥ 10%	1.68	1.19 to 2.38	.0035	1.38	0.96 to 1.99	.081
< 10%	Ref			Ref		
Body mass index						
Obese	1.62	1.03 to 2.53	.034	2.11	1.31 to 3.43	.0023
Overweight	1.17	0.81 to 1.71	.403	1.27	0.86 to 1.88	.231
Normal	Ref			Ref		

Abbreviations: HR, hazard ratio; Ref, reference (HR = 1.0).

*Adjusted for all variables shown in table.

Sensitivity analysis in the subgroup of patients (n = 625) who did not receive postoperative chemo- or radiotherapy yielded stable results: Among never smokers, obesity was associated with significantly worse DSS, as compared with normal weight (adjusted HR = 1.98; 95% CI, 1.15 to 3.42; $P = .014$).

DISCUSSION

Cigarette smoking status has been shown to attenuate the effect of BMI on mortality in prospective cohort studies, including death from multiple types of cancer.¹⁷⁻²⁰ However, smoking status has been infrequently accounted for in studies of EAC patients.^{26,27,39} Therefore, we examined the potential interaction between BMI and smoking in a large cohort of patients with EAC who underwent

potentially curative esophagectomy. We found that the prognostic impact of excess BMI significantly differed on the basis of smoking status (P for interaction = .023). This interaction indicates that stratification by or exclusion of smokers is necessary to determine the true prognostic impact of excess BMI and that simply adjusting for smoking as a confounder may fail to reveal this association in EAC. In never smokers, we found that obesity was associated with a two-fold increase in risk of death owing to EAC after adjusting for covariates. This adverse impact was limited to never smokers. By contrast, obesity was not prognostic among ever smokers and, in these patients, overweight status was shown to confer a protective effect of borderline statistical significance. Multiple studies have shown a favorable prognosis in overweight subjects,^{40,41} particularly in men,²⁰ which may be related to limitations of BMI versus

Table 3. Survival According to Body Mass Index Stratified by Smoking Status in Multivariable Models Adjusted for Age, Stage, Grade, Weight Loss, and Sex (N = 778)

Body Mass Index	No.	Disease-Specific Survival				Disease-Free Survival				Overall Survival			
		Event-Free Rate, %	HR	95% CI	<i>P</i>	Event-Free Rate, %	HR	95% CI	<i>P</i>	Event-Free Rate, %	HR	95% CI	<i>P</i>
Never smokers (n = 236)													
Obese	46	18	2.11	1.31 to 3.43	.002	15	2.03	1.30 to 3.18	.002	17	1.97	1.24 to 3.14	.004
Overweight	117	32	1.27	0.86 to 1.88	NS	28	1.16	0.81 to 1.67	NS	30	1.17	0.81 to 1.70	NS
Normal	73	36		Ref		28		Ref		32		Ref	
Ever smokers (n = 542)													
Obese	125	33	0.90	0.67 to 1.20	NS	27	1.00	0.76 to 1.33	NS	30	0.90	0.68 to 1.20	NS
Overweight	231	39	0.78	0.61 to 1.02	NS	34	0.87	0.68 to 1.11	NS	37	0.80	0.62 to 1.02	NS
Normal	186	28		Ref		23		Ref		26		Ref	

Abbreviations: HR, hazard ratio; NS, not statistically significant; Ref, reference (HR = 1.0).

Fig 2. Adjusted hazard ratios (HRs) for disease-specific survival after curative resection in 778 patients with esophageal adenocarcinoma according to body mass index (BMI) at the time of surgery, stratified by smoking status (P value for interaction between BMI and smoking status = .023). HRs are adjusted for tumor stage, grade, age, presurgical weight loss, and sex; 95% CIs and only significant P values ($< .05$) are shown.

direct measurements of body fat.⁴² Among never—but not ever—smokers, obesity doubled the risk of EAC recurrence or all-cause death. These novel observations underscore the importance of smoking status in the interpretation of BMI data and, to our knowledge, represent the first data showing that obesity adversely impacts survival in patients with EAC.

A complex interaction between BMI and smoking status has been increasingly appreciated, as smoking has been shown to be associated with reduced BMI and increased mortality risk.^{17-19,43} Consistent with our findings in patients with EAC, stronger associations between obesity and cancer-related or all-cause mortality have been observed in never, as compared with ever, smokers in multiple prospective cohort studies.¹⁷⁻²⁰ These studies indicate that the prognostic impact of BMI on mortality may be underestimated when combining data for smokers and nonsmokers, whereas mortality rates for never smokers seem to more accurately estimate the true prognostic impact of obesity. Accordingly, these findings^{17-20,43,44} support stratification by smoking status as performed in our study.

Studies in EAC and other cancers have shown that overweight status and/or obesity is associated with favorable survival as compared with normal weight, although results have been inconsistent.^{23,24,26} We found that overweight patients had favorable prognosis compared with normal weight patients that was of borderline statistical significance and limited to ever smokers. Notably, most patients with upper digestive cancers are overweight, not obese,^{45,46} and are ever smokers.^{47,48} In contrast to other studies, Cancer Prevention Study II (CPS II), a population-based US study, found a significant upward trend in cancer-related mortality risk as BMI increased above normal weight in patients with esophageal and gastric cancers.²⁰ However, unlike our study, CPS II included squamous cell carcinomas in its upper digestive cancer subpopulation, weight was collected at various time points relative to cancer diagnosis, and patients had heterogeneous stage and therapy. By contrast, our study cohort was homogeneous in that all patients had adenocarcinomas, and subcardial gastric cancers were excluded. Furthermore, body weight was recorded at cancer diagnosis,

and all patients underwent potentially curative esophagectomy. The majority of our study patients were male, which is consistent with the male predominance of EAC in the general population,^{6,49} and may potentially limit the applicability of our findings to women. In CPS II, the associations between obesity and cancer mortality were strongest in men, and a greater effect of excess weight on all-cause mortality in men has been observed in some,^{18,19} but not other,^{17,43} studies.

Mechanistic evidence has been reported, which may help explain the complex interaction between adiposity, smoking, nicotine, and tumor progression. Adiposity in overweight and obese patients has been linked to hyperinsulinemia and upregulation of insulin growth factor signaling and proinflammatory mediators, which may create a more favorable microenvironment for tumor cell survival, proliferation, and progression.⁵⁰ In addition, insulin-resistant adipocytes can activate macrophages that then release proinflammatory molecules, including tumor necrosis factor- α and interleukin-6, which in turn promote tumor growth.⁵¹⁻⁵³ In contrast to the carcinogenic effects of smoking, nicotine exposure may create a tumor microenvironment that is less favorable for progression of some tumor types. In this regard, nicotine exposure in both genetically obese and diet-induced obese mice has been shown to improve insulin sensitivity and to suppress the inflammation generated by adipose tissue.⁵⁴ Specifically, nicotine was shown to reduce tumor necrosis factor- α and interleukin-6 expression by epithelial cells of the human aerodigestive tract that are directly exposed to cigarette smoke.⁵⁵ Through its influence on the amount of circulating adipocyte-derived leptin and sensitivity to leptin, smoking may exert effects on energy metabolism and body weight, complicating the relationship between cancer and BMI. Smoking in humans can lower circulating leptin levels in a manner that is independent from the amount of body fat.⁵⁶ Leptin is increased in obese subjects and has been identified as a growth factor for cancers arising from the gastrointestinal epithelium.⁵⁷ Nicotine may also enhance the sensitivity of hypothalamic leptin receptors and increase appetite inhibition, resulting in reduced weight.⁵⁸ The withdrawal of this nicotinic mechanism with smoking cessation may help explain the frequent observation of weight gain in abstinent smokers.

Strengths of our study include measurement of BMI values by trained personnel at a uniform time point relative to diagnosis and treatment. Our study population was large and homogeneous with regard to histopathology and surgical therapy, with exclusion of patients receiving neoadjuvant therapy. Clinicopathologic and survival data were verified by review of individual patient records. Smoking data were collected using standard questionnaires, and our categorization of smoking (ie, never *v* ever) is in common usage, including prior studies in EAC,^{24,59} other cancers,²⁰ and other prognostic studies of BMI.^{17,18} The robustness of our findings is supported by the consistent associations across all three end points (ie, DSS, OS, DFS). Although retrospective design can weaken data collection, internal validity is preserved because ascertainment and collection of study variables (eg, pathologic stage, vital status) did not differ by BMI or smoking status. Our cohort is generalizable to other patients with EAC in the West by numerous parameters, including stage, age, and sex.⁶⁰

Limitations of our study include its retrospective design and the fact that, despite our large study population, only 171 patients (22%) were obese. Recognized limitations of BMI include the lack of a direct measure of central adiposity such as the waist-to-hip

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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