

Supplementary Material:

Title: Sex and smoking differences in the association between gastroesophageal reflux and risk of esophageal squamous cell carcinoma in a high-incidence area: Golestan Cohort Study.

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Supplementary Tables:

Table S1. Histologically confirmed ESCC tumor characteristics

	Entire cohort (n=290)	No GERD (Reference) (n=243)	Any GERD (n=47)	Mixed symptoms (n=34)	Heartburn only (n=13)
Location, n (%)					
Upper esophagus	30 (10.3%)	21 (8.6%)	9 (19.2%)	5 (14.7%)	4 (30.8%)
Mid esophagus	118 (40.7%)	95 (39.1%)	23 (48.9%)	17 (50.0%)	6 (46.2%)
Lower esophagus	107 (36.9%)	95 (39.1%)	12 (25.5%)	9 (26.5%)	3 (23.1%)
Unknown	35 (12.1%)	32 (13.2%)	3 (6.4%)	3 (8.8%)	0 (0.0%)
			*		*
Grade, n (%)					
Well differentiated	73 (25.2%)	63 (25.9%)	10 (21.3%)	8 (23.5%)	2 (15.4%)
Moderately differentiated	52 (17.9%)	43 (17.7%)	9 (19.2%)	7 (20.6%)	2 (15.4%)
Poorly differentiated	11 (3.8%)	9 (3.7%)	2 (4.3%)	2 (5.9%)	0 (0.0%)
Unknown	154 (53.1%)	128 (52.7%)	26 (55.3%)	17 (50.0%)	9 (69.2%)
Metastasis, n (%)					
Yes	13 (4.5%)	12 (4.9%)	1 (2.1%)	0 (0.0%)	1 (7.7%)
Unknown	277 (95.5%)	231 (95.1%)	46 (97.9%)	34 (100.0%)	12 (92.3%)

** p<0.01, *p<0.05

	Entire cohort (n=290)	Female (Reference) (n=141)	Male (n=149)
Location, n (%)			
Upper esophagus	30 (10.8%)	19 (13.5%)	11 (7.4%)
Mid esophagus	118 (40.7%)	59 (41.8%)	59 (39.6%)
Lower esophagus	107 (36.9%)	41 (29.1%)	66 (44.3%)
Unknown	35 (12.1%)	22 (15.6%)	13 (8.7%)
			*
Grade, n (%)			
Well differentiated	73 (25.2%)	36 (25.5%)	37 (24.8%)
Moderately differentiated	52 (17.9%)	22 (15.6%)	30 (20.1%)
Poorly differentiated	11 (3.8%)	6 (4.3%)	5 (3.4%)
Unknown	154 (53.1%)	77 (54.6%)	77 (51.7%)
Metastasis, n (%)			
Yes	13 (4.5%)	9 (6.4%)	4 (2.7%)
Unknown	277 (95.5%)	132 (93.6%)	145 (97.3%)

** p<0.01, *p<0.05

	Entire cohort (n=290)	Never Smoker (Reference) (n=231)	Ever Smoker (n=59)
Location, n (%)			
Upper esophagus	30 (10.8%)	30 (13.0%)	0 (0.0%)
Mid esophagus	118 (40.7%)	95 (41.1%)	23 (39.0%)
Lower esophagus	107 (36.9%)	77 (33.3%)	30 (50.9%)
Unknown	35 (12.1%)	29 (12.6%)	6 (10.2%)
			**
Grade, n (%)			
Well differentiated	73 (25.2%)	52 (22.5%)	21 (35.6%)
Moderately differentiated	52 (17.9%)	38 (16.5%)	14 (23.7%)
Poorly differentiated	11 (3.8%)	10 (4.3%)	1 (1.7%)
Unknown	154 (53.1%)	131 (56.7%)	23 (38.9%)
			*
Metastasis, n (%)			
Yes	13 (4.5%)	10 (4.3%)	3 (5.1%)
Unknown	277 (95.5%)	221 (95.7%)	56 (94.9%)

** p<0.01, *p<0.05

Table S2a. GERD Multivariable Logistic Regression, stratified by sex

	<u>Any GERD</u>		<u>Mixed symptoms</u>		<u>Heartburn alone</u>	
	Male	Female	Male	Female	Male	Female
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Age, per 10 year increase	0.97 (0.93-1.02)	1.07 (1.03-1.10)**	0.95 (0.90-1.00)	1.09 (1.04-1.13)**	1.02 (0.94-1.10)	1.01 (0.94-1.08)
Residence						
Rural	Reference	Reference	Reference	Reference	Reference	Reference
Urban	1.12 (0.99-1.28)	0.93 (0.86-1.02)	1.11 (0.95-1.29)	0.77 (0.70-0.85)**	1.18 (0.95-1.47)	1.63 (1.40-1.90) ²
Ethnicity						
Turkmen	Reference	Reference	Reference	Reference	Reference	Reference
Non-Turkmen	1.73 (1.57-1.90)**	1.46 (1.36-1.56)**	1.79 (1.61-2.00)**	1.48 (1.37-1.60)**	1.59 (1.34-1.87)**	1.42 (1.25-1.60)**
Socioeconomic status						
1 st quartile (lowest)	Reference	Reference	Reference	Reference	Reference	Reference
2 nd quartile	0.89 (0.79-0.99)	0.93 (0.87-1.01)	0.89 (0.78-1.02)	0.97 (0.89-1.06)	0.89 (0.73-1.08)	0.84 (0.73-0.97)
3 rd quartile	0.87 (0.78-0.97)	0.88 (0.81-0.95)	0.88 (0.77-1.00)	0.93 (0.86-1.02)	0.86 (0.71-1.04)	0.74 (0.64-0.86)
4 th quartile (highest)	0.60 (0.53-0.69) **	0.69 (0.63-0.75) **	0.56 (0.48-0.66) **	0.69 (0.63-0.77) **	0.69 (0.56-0.86) **	0.67 (0.57-0.79) **
BMI, n (%)						
< 18.5	1.03 (0.87-1.22)	1.12 (0.97-1.30)	1.11 (0.92-1.34)	1.11 (0.94-1.31)	0.87 (0.64-1.19)	1.17 (0.91-1.51)
18.5-24.9	Reference	Reference	Reference	Reference	Reference	Reference
25.0-29.9	1.08 (0.97-1.21)	0.90 (0.83-0.97)	1.01 (0.88-1.16)	0.89 (0.82-0.97)	1.25 (1.03-1.51)	0.92 (0.80-1.06)
>30	1.11 (0.95-1.31)	0.92 (0.85-1.01) *	1.05 (0.87-1.27)	0.93 (0.85-1.03)	1.27 (0.97-1.66) *	0.90 (0.77-1.05)
WHR, per SD	0.94 (0.88-0.99)*	1.11 (1.07-1.15)**	0.95 (0.89-1.01)	1.15 (1.10-1.19)**	0.91 (0.83-1.00)	1.01 (0.95-1.08)
Temperature of tea consumed						
< 60° C	Reference	Reference	Reference	Reference	Reference	Reference
≥ 60° C	1.06 (0.97-1.16)	1.05 (0.99-1.11)	1.05 (0.94-1.17)	0.99 (0.93-1.06)	1.08 (0.92-1.26)	1.26 (1.13-1.40)
Unknown	1.47 (1.04-2.09)	1.42 (1.11-1.81) *	1.65 (1.12-2.44)	1.47 (1.13-1.91)	1.05 (0.53-2.10)	1.22 (0.75-1.99) **
Fruit and vegetable consumption, n (%)						
1 st quintile (lowest)	Reference	Reference	Reference	Reference	Reference	Reference
2 nd quintile	0.88 (0.77-0.99)	0.87 (0.80-0.95)	0.88 (0.76-1.02)	0.89 (0.81-0.97)	0.86 (0.68-1.08)	0.84 (0.73-0.98)
3 rd quintile	0.86 (0.76-0.98)	0.82 (0.75-0.89)	0.88 (0.76-1.03)	0.84 (0.76-0.92)	0.81 (0.64-1.02)	0.77 (0.66-0.90)
4 th quintile	0.77 (0.67-0.88)	0.77 (0.70-0.84)	0.69 (0.58-0.80)	0.80 (0.72-0.88)	0.96 (0.77-1.20)	0.69 (0.59-0.82)
5 th quintile (highest)	0.67 (0.58-0.77)	0.67 (0.61-0.74)	0.60 (0.51-0.70)	0.67 (0.60-0.75)	0.84 (0.67-1.05)	0.69 (0.58-0.82)
Unknown	0.24 (0.14-0.42) **	0.21 (0.15-0.30) **	0.24 (0.13-0.45) **	0.22 (0.15-0.32) **	0.27 (0.09-0.70)	0.19 (0.09-0.41) **
Current exposure to indoor air pollution						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	0.96 (0.87-1.04)	0.96 (0.90-1.02)	0.90 (0.81-0.99)	0.89 (0.83-0.96)	1.09 (0.94-1.27)	1.21 (1.08-1.36)
Unknown	1.15 (0.70-1.88)	0.86 (0.67-1.10)	0.96 (0.51-1.79)	0.83 (0.63-1.09) **	1.52 (0.73-3.16)	0.99 (0.62-1.57) **
Current exposure to unpiped water						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.11 (0.99-1.25)	1.05 (0.97-1.13)	0.84 (0.72-0.97)	0.87 (0.80-0.95)	1.81 (1.53-2.15)	1.73 (1.51-1.97)
Unknown	1.03 (0.33-3.20)	0.76 (0.29-1.98)	0.64 (0.14-2.92) *	0.80 (0.29-2.23) **	2.40 (0.50-11.5) **	0.65 (0.08-5.13) **

	<u>Any GERD</u>		<u>Mixed symptoms</u>		<u>Heartburn alone</u>	
	Male aOR (95% CI)	Female aOR (95% CI)	Male aOR (95% CI)	Female aOR (95% CI)	Male aOR (95% CI)	Female aOR (95% CI)
Tooth loss						
Less than predicted	Reference	Reference	Reference	Reference	Reference	Reference
1-8 excess tooth loss	0.90 (0.81-0.99)	0.90 (0.83-0.96)	0.93 (0.82-1.05)	0.95 (0.87-1.02)	0.82 (0.68-0.98)	0.76 (0.66-0.87)
>9 excess tooth loss	1.03 (0.92-1.13)	0.95 (0.88-1.02)	1.03 (0.91-1.16)	0.98 (0.91-1.06)	1.01 (0.85-1.21)	0.85 (0.75-0.97) **
Ever smoked tobacco use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Former	1.11 (0.99-1.25)	1.30 (0.98-1.72)	1.13 (0.98-1.30)	1.35 (0.99-1.83)	1.06 (0.86-1.31)	1.13 (0.66-1.93)
Current	1.16 (1.04-1.29) **	1.06 (0.87-1.28)	1.10 (0.97-1.25)	1.10 (0.90-1.36)	1.27 (1.07-1.52) **	0.90 (0.63-1.29)
Ever opium use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.58 (1.43-1.74)**	1.49 (1.35-1.64)**	1.62 (1.45-1.82)**	1.55 (1.39-1.73)**	1.49 (1.26-1.75)**	1.29 (1.08-1.56)**
NSAID use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.25 (1.10-1.42)**	1.35 (1.24-1.46)**	1.25 (1.07-1.46)**	1.37 (1.25-1.50)**	1.25 (1.01-1.55)*	1.27 (1.09-1.47)**

Adjusted by age, urban residency, ethnicity, socioeconomic status, waist-to-hip ratio, body mass index, hot tea consumption, fruit and vegetable consumption, unpiped water exposure, tooth loss, tobacco smoking, opiate use, and non-steroidal anti-inflammatory drug use.

** p<0.01, *p<0.05

Table S2b. GERD Multivariable Logistic Regression, stratified by tobacco smoking

	<u>Any GERD</u>		<u>Mixed symptoms</u>		<u>Heartburn alone</u>	
	<u>Nonsmoker</u> aOR (95% CI)	<u>Smoker</u> aOR (95% CI)	<u>Nonsmoker</u> aOR (95% CI)	<u>Smoker</u> aOR (95% CI)	<u>Nonsmoker</u> aOR (95% CI)	<u>Smoker</u> aOR (95% CI)
Age, per 10 year increase	1.05 (1.02-1.09)**	0.93 (0.87-0.99)*	1.06 (1.03-1.10)**	0.94 (0.87-1.01)	1.03 (0.97-1.08)	0.92 (0.82-1.03)
Sex, n (%)						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	2.26 (2.11-2.41)**	2.07 (1.73-2.47)**	2.49 (2.31-2.69)**	2.27 (1.87-2.77)**	1.73 (1.55-1.94)**	1.53 (1.10-2.13)*
Residence						
Rural	Reference	Reference	Reference	Reference	Reference	Reference
Urban	0.96 (0.89-1.04)	1.13 (0.96-1.34)	0.82 (0.75-0.90)**	1.07 (0.87-1.30)	1.49 (1.29-1.71)**	1.33 (0.99-1.77)
Ethnicity						
Turkmen	Reference	Reference	Reference	Reference	Reference	Reference
Non-Turkmen	1.55 (1.46-1.65)**	1.49 (1.30-1.71)**	1.57 (1.47-1.68)**	1.58 (1.35-1.84)**	1.51 (1.36-1.69)**	1.29 (1.02-1.64)*
Socioeconomic status						
1 st quartile (lowest)	Reference	Reference	Reference	Reference	Reference	Reference
2 nd quartile	0.92 (0.86-0.99)	0.91 (0.78-1.06)	0.96 (0.89-1.04)	0.88 (0.73-1.05)	0.83 (0.73-0.94)	0.97 (0.74-1.27)
3 rd quartile	0.88 (0.82-0.95)	0.86 (0.74-1.00)	0.93 (0.86-1.01)	0.84 (0.70-1.01)	0.76 (0.67-0.86)	0.91 (0.70-1.20)
4 th quartile (highest)	0.66 (0.61-0.72) **	0.62 (0.52-0.75) **	0.67 (0.61-0.73) **	0.58 (0.46-0.72) **	0.66 (0.57-0.77) **	0.74 (0.54-1.02)
BMI, n (%)						
< 18.5	1.07 (0.94-1.22)	1.15 (0.95-1.40)	1.10 (0.94-1.28)	1.19 (0.95-1.49)	1.02 (0.81-1.30)	1.09 (0.77-1.54)
18.5-24.9	Reference	Reference	Reference	Reference	Reference	Reference
25.0-29.9	0.91 (0.85-0.97)	1.13 (0.96-1.32)	0.89 (0.82-0.96)	1.06 (0.88-1.28)	0.97 (0.86-1.10)	1.29 (0.99-1.69)
>30	0.95 (0.88-1.03)	1.03 (0.82-1.30)	0.95 (0.87-1.04)	0.97 (0.74-1.27)	0.96 (0.83-1.11)	1.18 (0.80-1.02)
WHR, per SD	1.07 (1.04-1.11) ²	0.99 (0.92-1.07)	1.11 (1.07-1.15) ²	1.01 (0.92-1.10)	0.99 (0.93-1.05)	0.94 (0.83-1.07)
Temperature of tea consumed						
< 60° C	Reference	Reference	Reference	Reference	Reference	Reference
≥ 60° C	1.08 (1.03-1.14)	0.91 (0.81-1.04)	1.03 (0.97-1.10)	0.87 (0.75-1.00)	1.23 (1.12-1.36)	1.03 (0.83-1.28)
Unknown	1.55 (1.26-1.91) **	0.78 (0.40-1.53)	1.64 (1.30-2.06) *	0.88 (0.42-1.83)	1.28 (0.85-1.93) **	0.43 (0.09-2.16)
Fruit and vegetable consumption, n (%)						
1 st quintile (lowest)	Reference	Reference	Reference	Reference	Reference	Reference
2 nd quintile	0.89 (0.82-0.96)	0.81 (0.68-0.97)	0.90 (0.82-0.98)	0.84 (0.69-1.03)	0.87 (0.76-0.99)	0.75 (0.55-1.02)
3 rd quintile	0.83 (0.77-0.90)	0.80 (0.67-0.96)	0.85 (0.78-0.93)	0.86 (0.70-1.05)	0.80 (0.69-0.92)	0.67 (0.49-0.93)
4 th quintile	0.77 (0.71-0.84)	0.73 (0.61-0.88)	0.77 (0.71-0.85)	0.68 (0.55-0.84)	0.76 (0.66-0.88)	0.86 (0.64-1.17)
5 th quintile (highest)	0.69 (0.63-0.75)	0.57 (0.47-0.69)	0.67 (0.60-0.74)	0.51 (0.41-0.64)	0.75 (0.64-0.87)	0.70 (0.51-0.95)
Unknown	0.21 (0.16-0.29) **	0.61 (0.13-0.54) **	0.22 (0.16-0.32) **	0.22 (0.09-0.55) **	0.18 (0.09-0.36) **	0.38 (0.12-1.21)
Current exposure to indoor air pollution						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	0.98 (0.93-1.14)	0.86 (0.76-0.97)	0.91 (0.85-0.97)	0.84 (0.72-0.96)	1.23 (1.11-1.36)	0.92 (0.74-1.14)
Unknown	0.89 (0.71-1.62)	1.13 (0.58-2.22) *	0.85 (0.65-1.11) **	0.97 (0.43-2.20) *	1.05 (0.69-1.60) **	1.47 (0.52-4.14)
Current exposure to unpiped water						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.07 (0.99-1.14)	1.07 (0.91-1.25)	0.86 (0.79-0.94)	0.84 (0.69-1.03)	1.78 (1.58-1.99)	1.68 (1.31-2.16)
Unknown	0.72 (0.32-1.62)	2.23 (0.40-12.5)	0.65 (0.26-1.63) **	1.53 (0.16-14.6)	0.94 (0.21-4.15) **	6.07 (0.50-73.1) **

	<u>Any GERD</u>		<u>Mixed symptoms</u>		<u>Heartburn alone</u>	
	Nonsmoker aOR (95% CI)	Smoker aOR (95% CI)	Nonsmoker aOR (95% CI)	Smoker aOR (95% CI)	Nonsmoker aOR (95% CI)	Smoker aOR (95% CI)
Tooth loss						
Less than predicted	Reference	Reference	Reference	Reference	Reference	Reference
1-8 excess tooth loss	0.93 (0.87-0.99)	0.81 (0.70-0.93)	0.98 (0.91-1.05)	0.82 (0.69-0.97)	0.79 (0.70-0.89)	0.77 (0.60-0.99)
>9 excess tooth loss	0.98 (0.92-1.05)	0.93 (0.81-1.72)	1.01 (0.94-1.09)	0.92 (0.78-1.07)	0.90 (0.80-1.01)	0.97 (0.77-1.22)
					*	
Ever opium use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.56 (1.43-1.69)**	1.49 (1.32-1.68)**	1.62 (1.47-1.78)**	1.52 (1.32-1.75)**	1.38 (1.18-1.60)**	1.43 (1.16-1.75)**
NSAID use						
No	Reference	Reference	Reference	Reference	Reference	Reference
Yes	1.34 (1.24-1.45)**	1.23 (1.04-1.45)*	1.37 (1.26-1.49)**	1.18 (0.97-1.43)	1.25 (1.09-1.43)**	1.34 (1.02-1.76)*

Adjusted by age, sex urban residency, ethnicity, socioeconomic status, waist-to-hip ratio, body mass index, hot tea consumption, fruit and vegetable consumption, unpiped water exposure, tooth loss, opiate use, and non-steroidal anti-inflammatory drug use.

** p<0.01, *p<0.05

Table S3. ESCC Risk Analysis – GERD symptom severity and duration

	Overall	
	Crude HR (95% CI)	aHR (95% CI)
GERD symptom severity		
No symptoms	Reference	Reference
Mild-moderate symptoms	0.83 (0.65-1.06)	0.87 (0.68-1.11)
Severe symptoms	0.90 (0.60-1.34)	0.90 (0.60-1.36)
GERD duration		
No symptoms	Reference	Reference
< 1 year	0.71 (0.46-1.10)	0.75 (0.48-1.17)
1-5 years	0.76 (0.56-1.03)	0.82 (0.60-1.11)
> 5 years	1.01 (0.76-1.34)	1.04 (0.78-1.38)
GERD severity + duration		
No symptoms	Reference	Reference
Mild-mod and < 1 year	0.73 (0.46-1.16)	0.77 (0.48-1.22)
Mild-mod and 1-5 years	0.74 (0.53-1.03)	0.79 (0.57-1.09)
Mild-mod and > 5 years	0.99 (0.73-1.34)	1.01 (0.74-1.37)
Severe and < 1 year	0.43 (0.11-1.74)	0.45 (0.11-1.81)
Severe and 1-5 years	0.85 (0.45-1.62)	0.89 (0.46-1.69)
Severe and > 5 years	1.10 (0.66-1.83)	1.07 (0.64-1.78)

Adjusted by age, sex, ethnicity, socioeconomic status, body mass index, tobacco smoking, and opiate use.

** p<0.01, *p<0.05

	Male		Female	
	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR (95% CI)
GERD symptom severity				
No symptoms	Reference	Reference	Reference	Reference
Mild-moderate symptoms	0.76 (0.54-1.06)	0.81 (0.58-1.14)	1.00 (0.70-1.43)	0.94 (0.65-1.34)
Severe symptoms	0.99 (0.53-1.85)	0.98 (0.52-1.85)	1.02 (0.60-1.75)	0.89 (0.52-1.53)
GERD duration				
No symptoms	Reference	Reference	Reference	Reference
< 1 year	0.92 (0.50-1.69)	0.94 (0.51-1.74)	0.66 (0.35-1.25)	0.63 (0.34-1.18)
1-5 years	0.67 (0.43-1.05)	0.75 (0.48-1.18)	0.91 (0.59-1.41)	0.88 (0.57-1.36)
> 5 years	0.95 (0.64-1.41)	1.06 (0.71-1.57)	1.17 (0.78-1.75)	1.05 (0.70-1.58)
GERD severity + duration				
No symptoms	Reference	Reference	Reference	Reference
Mild-mod and < 1 year	0.86 (0.45-1.66)	0.88 (0.45-1.69)	0.74 (0.39-1.42)	0.70 (0.37-1.35)
Mild-mod and 1-5 years	0.67 (0.42-1.07)	0.73 (0.45-1.17)	0.89 (0.56-1.42)	0.86 (0.54-1.37)
Mild-mod and > 5 years	0.85 (0.55-1.33)	0.93 (0.60-1.46)	1.22 (0.79-1.89)	1.10 (0.72-1.71)
Severe and < 1 year	0.74 (0.10-5.34)	0.68 (0.09-4.88)	0.37 (0.05-2.67)	0.34 (0.05-2.45)
Severe and 1-5 years	0.68 (0.22-2.16)	0.73 (0.23-2.32)	1.12 (0.51-2.46)	1.01 (0.46-2.22)
Severe and > 5 years	1.35 (0.62-2.93)	1.31 (0.60-2.85)	1.17 (0.60-2.30)	0.98 (0.50-1.94)

Adjusted by age, ethnicity, socioeconomic status, body mass index, tobacco smoking, and opiate use.

** p<0.01, *p<0.05

Table S4. Sensitivity Analysis – Exclude all ESCC dx within 2 years after enrollment

	Overall	
	Crude HR (95% CI)	aHR (95% CI)
Any GERD	0.84 (0.60-1.18)	0.86 (0.61-1.21)
Mixed symptoms	0.81 (0.55-1.21)	0.83 (0.56-1.24)
Heartburn alone	0.92 (0.52-1.65)	0.94 (0.52-1.68)

Adjusted by age, sex, ethnicity, socioeconomic status, body mass index, tobacco smoking, and opiate use.

** p<0.01, *p<0.05

	Male		Female	
	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR (95% CI)
Any GERD	0.46 (0.23-0.94)*	0.48 (0.23-0.98)*	1.19 (0.80-1.78)	1.11 (0.74-1.67)
Mixed symptoms	0.34 (0.13-0.93)	0.36 (0.13-0.97)	1.20 (0.77-1.88)	1.10 (0.70-1.72)
Heartburn alone	0.71 (0.26-1.93)	0.72 (0.26-1.94)	1.18 (0.58-2.43)	1.13 (0.55-2.32)

Adjusted by age, ethnicity, socioeconomic status, body mass index, tobacco smoking, and opiate use.

** p<0.01, *p<0.05

	Never Smoker		Ever Smoker	
	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR (95% CI)
Any GERD	0.96 (0.67-1.37)	1.00 (0.70-1.44)	0.35 (0.11-1.12)	0.31 (0.10-1.01)
Mixed symptoms	0.92 (0.61-1.39)	0.97 (0.64-1.47)	0.34 (0.08-1.39)	0.28 (0.07-1.17)
Heartburn alone	1.06 (0.58-1.96)	1.09 (0.59-2.01)	0.37 (0.05-2.72)	0.38 (0.05-2.78)

Adjusted by age, sex, ethnicity, socioeconomic status, body mass index, and opiate use.

** p<0.01, *p<0.05

Table S5. Sensitivity Analysis – Exclude all ESCC dx within 2 years after enrollment, but include all esophageal cancer tumors

	Overall	
	Crude HR (95% CI)	aHR (95% CI)
Any GERD	0.90 (0.66-1.23)	0.92 (0.67-1.25)
Mixed symptoms	0.88 (0.62-1.26)	0.90 (0.62-1.29)
Heartburn alone	0.96 (0.56-1.65)	0.97 (0.56-1.66)

Adjusted by age, sex, ethnicity, socioeconomic status, body mass index, tobacco smoking, and opiate use.

** p<0.01, *p<0.05

	Male		Female	
	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR (95% CI)
Any GERD	0.50 (0.26-0.95)*	0.50 (0.26-0.95)*	1.32 (0.91-1.92)	1.22 (0.84-1.78)
Mixed symptoms	0.44 (0.20-1.00)	0.44 (0.20-1.01)	1.31 (0.86-1.98)	1.18 (0.78-1.81)
Heartburn alone	0.62 (0.23-1.67)	0.60 (0.22-1.63)	1.38 (0.72-2.64)	1.31 (0.68-2.51)

Adjusted by age, ethnicity, socioeconomic status, body mass index, tobacco smoking, and opiate use.

** p<0.01, *p<0.05

	Never Smoker		Ever Smoker	
	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR (95% CI)
Any GERD	1.07 (0.77-1.48)	1.11 (0.80-1.56)	0.35 (0.13-0.98)	0.31 (0.11-0.86)*
Mixed symptoms	1.03 (0.70-1.50)	1.09 (0.73-1.59)	0.39 (0.12-1.23)	0.31 (0.10-1.01)
Heartburn alone	1.18 (0.67-2.07)	1.20 (0.68-2.11)	0.29 (0.04-2.07)	0.29 (0.04-2.08)

Adjusted by age, sex, ethnicity, socioeconomic status, body mass index, and opiate use.

** p<0.01, *p<0.05