Table ST1: Comparison of baseline characteristics between included and excluded subjects.

Variables	Total N = 12,373	Included N = 9,660	Excluded N = 2,713	P-value
Age (Years) - Mean (SD)	63(13.8)	63(13.5)	63(14.9)	0.07
Median	63	64	63	
10th - 90th percentile	44-81	45 - 80	43-82	
Follow Up (Years) – Mean (SD)	4.9(3.5)	4.8(3.3)	5.6(3.9)	<0.001
		N (%)		
Gender (Male)	7,905 (63.89%)	6,042 (62.55%)	1,863 (68.67%)	<0.001
Ever smoker*	6,251 (52.09%)	4,940 (51.91%)	1,311 (52.80%)	0.428
Hiatal Hernia	2,517 (20.34%)	2,058 (21.30%)	459 (16.92%)	<0.001
Diabetes	705 (5.70%)	651 (6.74%)	54 (1.99%)	<0.001
PPIs	10,341 (83.58%)	8,177 (84.65%)	2,164 (79.76%)	<0.001
NSAIDs	7,529 (60.85%)	6,015 (62.27%)	1,514 (55.81%)	<0.001
Statins	3,016 (24.38%)	2,668 (27.62%)	348 (12.83%)	<0.001
Metformin	680 (5.50%)	630 (6.52%)	50 (1.84%)	<0.001
Insulin	238 (1.92%)	226 (2.34%)	12 (0.44%)	<0.001
OAD	841 (6.80%)	767 (7.94%)	74 (2.73%)	<0.001

*Smoking percentages were taken among patients without missing information, so percentages are not reflective of the total.

Supplementary table ST2:

Effect of PPI dosage (once a day versus twice a day) on risk of progression from BE to esophageal carcinoma.

Drugs	Multivariate Analysis	
	HR (95% CI)	P value
PPI 1 QD	1.13 (0.63, 2.03)	0.688
PPI BID	0.97 (0.51, 1.86)	0.93
NSAIDs	0.95 (0.63, 1.42)	0.79
Statins	0.60 (0.34, 1.09)	0.095
Metformin	0.50 (0.09, 2.78)	0.431
Insulin	.58 (0.10, 3.42)	0.55
OAD	3.49 (0.84, 14.49)	0.085

Supplementary table ST3a:

Effect of varying definitions of incident cancer from 6m to 18 m on associations with demographic variables.

Variables	Univariate Analysis		> 12 months Multivariate Analysis		> 6 months Multivariate Analysis		> 18 months Multivariate Analysis	
	HR (95% CL)	P Value	HR (95% CL)	P Value	HR (95% CL)	P Value	HR (95% CL)	P Value
Age (per yr)	1.03 (1.01, 1.04)	0.001	1.04 (1.02, 1.05)	<0.0001	1.04 (1.02, 1.05)	<0.0001	1.04 (1.02, 1.05)	<0.0001
Male sex	2.39 (1.48, 3.87)	<0.0001	2.79 (1.69, 4.62)	<0.0001	2.83 (1.77, 4.53)	<0.0001	2.79 (1.68, 4.62)	<0.0001
Ever smoker	1.22 (0.82, 1.82)	0.317	1.08 (0.71, 1.63)	0.722	1.17 (0.79, 1.72)	0.441	1.06 (0.70, 1.61)	0.781
Ever drinker	0.72 (0.35, 1.49)	0.377	XX	XX	XX	XX	XX	XX
BMI (normal)	Reference							
Overweight (BMI 25-29.9)	1.55 (0.97, 2.47)	0.067	1.54 (0.96, 2.48)	0.072	1.57 (1.01, 2.44)	0.044	1.61 (1.00, 2.59)	0.052
Obese I (BMI 30-34.9)	1.30 (0.72, 2.34)	0.389	1.70 (0.92, 3.13)	0.091	1.77 (1.02, 3.09)	0.043	1.77 (0.96, 3.28)	0.069
Obese II (BMI > 34.9)	1.30 (0.18, 9.47)	0.799	2.22 (0.30, 16.62)	0.437	1.98 (0.27, 14.57)	0.504	2.35 (0.31, 17.64)	0.405
Hiatal Hernia	1.00 (0.62, 1.63)	0.987	0.99 (0.61, 1.60)	0.958	1.00 (0.65, 1.56)	0.983	0.99 (0.61, 1.6)	0.954
Diabetes	0.61 (0.19, 1.94)	0.404	0.33 (0.06, 1.85)	0.207	0.38 (0.08, 1.90)	0.237	0.33 (0.06, 1.86)	0.208

Supplementary Table ST3b. Effect of varying definitions of incident cancer from 6m to 18 m on associations with medications (conventional models).

Drugs	Univariate Analysis		Multivariate Analysis > 12 months		Multivariate Analysis > 6 months		Multivariate Analysis > 18 months	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.98 (0.57, 1.69)	0.938	1.05 (0.59, 1.86)	0.86	1.03 (0.61, 1.73)	0.91	1.13 (0.63, 2.04)	0.677
NSAIDs	0.94 (0.63, 1.40)	0.746	0.94 (0.63, 1.41)	0.77	0.92 (0.63, 1.33)	0.651	0.92 (0.61, 1.38)	0.687
Statins	0.75 (0.44, 1.30)	0.309	0.61 (0.34, 1.10)	0.102	0.72 (0.44, 1.18)	0.197	0.62 (0.34, 1.11)	0.11
Metformin	0.64 (0.20, 2.02)	0.449	0.51 (0.09, 2.81)	0.437	0.60 (0.12, 2.98)	0.53	0.51 (0.09, 2.84)	0.44
Insulin	0.65 (0.09, 4.68)	0.673	0.57 (0.10, 3.35)	0.537	0.50 (0.09, 2.90)	0.44	0.58 (0.10, 3.37)	0.541
OAD	0.85 (0.35, 2.10)	0.732	3.38 (0.82, 13.95)	0.092	2.60 (0.60, 11.33)	0.202	3.41 (0.83, 14.04)	0.09

Supplementary Table ST3c. Effect of varying definitions of incident cancer from 6m to 18 m on associations with medications (time varying models).

Time varying	> 12 months		> 6 months		> 18 months	
Drugs	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.43 (0.36, 0.52)	<0.0001	0.40 (0.32, 0.49)	<0.0001	0.43 (0.36, 0.52)	<0.0001
NSAIDs	0.15 (0.01, 1.86)	0.14	0.12 (0.01, 1.72)	0.118	0.16 (0.01, 1.88)	0.144
Statins	0.61 (0.45, 0.83)	0.002	0.59 (0.42, 0.81)	0.001	0.61 (0.45, 0.83)	0.002
Metformin	0.57 (0.27, 1.21)	0.142	0.55 (0.25, 1.22)	0.142	0.57 (0.27, 1.2)	0.142
Insulin	xx	xx	xx	xx	xx	xx
OAD	1.26 (0.89, 1.78)	0.193	1.26 (0.88, 1.79)	0.206	1.26 (0.89, 1.79)	0.187

Definition for incident vs prevalent esophageal cancer	> 12 months		> 6 months		> 18 months	
Incidence of esophageal cancer (per 1000 patient-yrs of follow up)	2.23 (1.84, 2.71)		2.60 (2.23, 3.04)		2.17 (1.84, 2.58)	
Variables	**Univariate Analysis**		**Multivariate Analysis**		**Multivariate Analysis**		**Multivariate Analysis**	
	HR (95% CL)	P Value	HR (95% CL)	P Value	HR (95% CL)	P Value	HR (95% CL)	P Value
Age (per yr)	1.03 (1.01, 1.04)	0.001	1.04 (1.02, 1.05)	<0.0001	1.04 (1.02, 1.05)	<0.0001	1.04 (1.02, 1.05)	<0.0001
Male sex	2.39 (1.48, 3.87)	<0.0001	2.79 (1.69, 4.62)	<0.0001	2.83 (1.77, 4.53)	<0.0001	2.79 (1.68, 4.62)	<0.0001
Ever smoker	1.22 (0.82, 1.82)	0.317	1.08 (0.71, 1.63)	0.722	1.17 (0.79, 1.72)	0.441	1.06 (0.70, 1.61)	0.781
Ever drinker	0.72 (0.35, 1.49)	0.377	XX	XX	XX	XX	XX	XX
BMI (normal)	Reference							
Overweight (BMI 25-29.9)	1.55 (0.97, 2.47)	0.067	1.54 (0.96, 2.48)	0.072	1.57 (1.01, 2.44)	0.044	1.61 (1.00, 2.59)	0.052
Obese I (BMI 30-34.9)	1.30 (0.72, 2.34)	0.389	1.70 (0.92, 3.13)	0.091	1.77 (1.02, 3.09)	0.043	1.77 (0.96, 3.28)	0.069
Obese II (BMI > 34.9)	1.30 (0.18, 9.47)	0.799	2.22 (0.30, 16.62)	0.437	1.98 (0.27, 14.57)	0.504	2.35 (0.31, 17.64)	0.405
Hiatal Hernia	1.00 (0.62, 1.63)	0.987	0.99 (0.61, 1.60)	0.958	1.00 (0.65, 1.56)	0.983	0.99 (0.61, 1.6)	0.954
Diabetes	0.61 (0.19, 1.94)	0.404	0.33 (0.06, 1.85)	0.207	0.38 (0.08, 1.90)	0.237	0.33 (0.06, 1.86)	0.208

Supplementary table ST4b. Effect of excluding a proportion of subjects with BE who may not

have intestinal metaplasia on histology, on associations with medications (conventional

analysis).

			> 12 months		Removed 36%	
					> 12 months	
Drugs	**Univariate Analysis**		**Multivariate Analysis (Randomly removing 7% of cancers)**		**Multivariate Analysis (Randomly removing 7% of cancers)**	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.98 (0.57, 1.69)	0.938	1.05 (0.59, 1.86)	0.86	1.24 (0.58, 2.66)	0.585
NSAIDs	0.94 (0.63, 1.40)	0.746	0.94 (0.63, 1.41)	0.77	0.86 (0.51, 1.44)	0.556
Statins	0.75 (0.44, 1.30)	0.309	0.61 (0.34, 1.10)	0.102	0.82 (0.41, 1.66)	0.586
Metformin	0.64 (0.20, 2.02)	0.449	0.51 (0.09, 2.81)	0.437	0.16 (0.02, 1.56)	0.115
Insulin	0.65 (0.09, 4.68)	0.673	0.57 (0.10, 3.35)	0.537	01.20 (0.29, 5.05)	0.803
OAD	0.85 (0.35, 2.10)	0.732	3.38 (0.82, 13.95)	0.092	2.91 (0.68, 12.49)	0.15

Supplementary Table ST4c. Effect of excluding a proportion of subjects with BE who may not have intestinal metaplasia on histology, on associations with medications (time varying analysis).

			Removed 36%	
Time varying	> 12 months		> 12 months	
Drugs	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.43 (0.36, 0.52)	<0.0001	0.42 (0.32, 0.54)	<0.0001
NSAIDs	0.15 (0.01, 1.86)	0.14	0.32 (0.04, 2.74)	0.299
Statins	0.61 (0.45, 0.83)	0.002	0.67 (0.48, 0.93)	0.016
Metformin	0.57 (0.27, 1.21)	0.142	0.71 (0.28, 1.80)	0.469
Insulin	xx	xx		
OAD	1.26 (0.89, 1.78)	0.193	1.18 (0.62, 2.24)	0.614

Supplementary Table ST5a: Comparison of Predictors of Progression to Esophageal Carcinoma: Demographic and lifestyle factors between complete cohort and that included without any missing values.

Variables	Total Sample (12,373)				Included Study Sample (9,660)			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CL)	P Value	HR (95% CL)	P value	HR (95% CL)	P Value	HR (95% CL)	P Value
Age (per yr)	1.03 (1.02, 1.04)	<0.001	1.04 (1.03, 1.05)	<0.001	1.03 (1.01, 1.04)	<0.0001	1.04 (1.02, 1.05)	<0.0001
Male sex	2.55 (1.91, 3.41)	<0.001	3.13 (2.33, 4.21)	<0.001	2.48 (1.53, 4.0)	<0.0001	2.93 (1.81, 4.74)	<0.0001
Ever smoker	1.18 (0.93, 1.49)	0.176	1.28 (0.17, 9.34)	0.81	1.22 (0.82, 1.82)	0.317	1.08(0.71, 1.63)	0.722
BMI (normal)					Reference			
Overweight (BMI 25-29.9)					1.64 (1.03, 2.60)	0.037	1.63 (1.02, 2.61)	0.040
Obese I (BMI 30-34.9)					1.30 (0.72, 2.35)	0.383	1.71 (0.93, 3.17)	0.084
Obese II (BMI > 34.9)					1.28 (0.17, 9.34)	0.810	2.24(0.30, 16.81)	0.436
Hiatal Hernia	1.11 (0.85,	0.445	1.22 (0.93,	0.155	0.97	0.894	0.97	0.899

| | 1.46) | | 1.62) | | (0.60, 1.56) | | (0.60, 1.57) | |
| Diabetes | 0.95 (0.56, 1.63) | 0.865 | 0.64 (0.23, 1.75) | 0.385 | 0.60 (0.19, 1.89) | 0.382 | 0.33 (0.059, 1.87) | 0.211 |

Supplementary Table ST5b: Comparison of Predictors of Progression to Esophageal Carcinoma – Medications between complete cohort and cohort with no missing variables.

Drugs	Total Sample (12,373)				Included Study Sample (9,660)			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.67 (0.51, 0.88)	0.004	0.69 (0.52, 0.92)	0.011	0.88 (0.52, 1.47)	0.617	0.94 (0.55, 1.60)	0.816
NSAIDs	1.07 (0.85, 1.36)	0.544	1.13 (0.89, 1.43)	0.319	0.91 (0.61, 1.35)	0.645	0.93 (0.63, 1.37)	0.707
Statins	1.18 (0.91, 1.54)	0.216	0.96 (0.73, 1.28)	0.797	0.73 (0.43, 1.26)	0.264	0.59 (0.32, 1.07)	0.080
Metformin	0.85 (0.48, 1.51)	0.580	0.57 (0.22, 1.45)	0.238	0.63 (0.20, 1.97)	0.425	0.45 (0.86, 2.40)	0.353
Insulin	0.63 (0.20, 1.95)	0.419	0.56 (0.18, 1.73)	0.317	0.64 (0.09, 4.58)	0.658	0.76 (0.11, 5.17)	0.781
OAD	1.02 (0.64, 1.65)	0.923	2.09 (0.69, 6.30)	0.192	0.83 (0.34, 2.05)	0.691	1.54 (0.46, 5.18)	0.486

Supplementary table ST6a. Analysis of associations with demographic variables in a subset of BE patients who have not have surveillance endoscopy in the last 3 years (as a surrogate marker for BE patients without dysplasia).

					< 1 Endo in past 3 yr	
			> 12 months		> 12 months	
Variables	**Univariate Analysis**		**Multivariate Analysis**		**Multivariate Analysis**	
	HR (95% CL)	P Value	HR (95% CL)	P Value	HR (95% CL)	P Value
Age (per yr)	1.03 (1.01, 1.04)	0.001	1.04 (1.02, 1.05)	<0.0001	1.03 (1.02, 1.05)	<0.0001
Male sex	2.39 (1.48, 3.87)	<0.0001	2.79 (1.69, 4.62)	<0.0001	2.63 (1.57, 4.41)	<0.0001
Ever smoker	1.22 (0.82, 1.82)	0.317	1.08 (0.71, 1.63)	0.722	1.03 (0.67, 1.59)	0.878
Ever drinker	0.72 (0.35, 1.49)	0.377	XX	XX	XX	XX
BMI (normal)	Reference					
Overweight (BMI 25-29.9)	1.55 (0.97, 2.47)	0.067	1.54 (0.96, 2.48)	0.072	1.60 (0.97, 2.64)	0.066
Obese I (BMI 30-34.9)	1.30 (0.72, 2.34)	0.389	1.70 (0.92, 3.13)	0.091	1.64 (0.86, 3.15)	0.135
Obese II (BMI > 34.9)	1.30 (0.18, 9.47)	0.799	2.22 (0.30, 16.62)	0.437	2.26 (0.30, 17.24)	0.432
Hiatal Hernia	1.00 (0.62, 1.63)	0.987	0.99 (0.61, 1.60)	0.958	0.92 (0.54, 1.55)	0.741
Diabetes	0.61 (0.19, 1.94)	0.404	0.33 (0.06, 1.85)	0.207	0.54 (0.04, 6.93)	0.639

Supplementary table ST6b. Analysis of associations with medications (conventional analysis) in a subset of BE patients who have not have surveillance endoscopy in the last 3 years (as a surrogate marker for BE patients without dysplasia).

Drugs	Univariate Analysis		> 12 months Multivariate Analysis		< 1 Endo in past 3 yr Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.98 (0.57, 1.69)	0.938	1.05 (0.59, 1.86)	0.86	1.05 (0.59, 1.87)	0.868
NSAIDs	0.94 (0.63, 1.40)	0.746	0.94 (0.63, 1.41)	0.77	0.96 (0.63, 1.46)	0.841
Statins	0.75 (0.44, 1.30)	0.309	0.61 (0.34, 1.10)	0.102	0.66 (0.36, 1.22)	0.187
Metformin	0.64 (0.20, 2.02)	0.449	0.51 (0.09, 2.81)	0.437	1.02 (0.08, 13.05)	0.987
Insulin	0.65 (0.09, 4.68)	0.673	0.57 (0.10, 3.35)	0.537	XX	XX
OAD	0.85 (0.35, 2.10)	0.732	3.38 (0.82, 13.95)	0.092	1.17 (0.18, 7.85)	0.868

Supplementary table ST6c. Analysis of associations with medications (time varying analysis) in a subset of BE patients who have not have surveillance endoscopy in the last 3 years (as a surrogate marker for BE patients without dysplasia).

Time varying	> 12 months		< 1 Endo in past 3 yr	
Drugs	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.43 (0.36, 0.52)	<0.0001	0.42 (0.34, 0.52)	<0.0001
NSAIDs	0.15 (0.01, 1.86)	0.14	0.17 (0.01, 2.00)	0.16
Statins	0.61 (0.45, 0.83)	0.002	0.63 (0.46, 0.85)	0.003
Metformin	0.57 (0.27, 1.21)	0.142	0.59 (0.29, 1.21)	0.152
Insulin	xx	xx	xx	xx
OAD	1.26 (0.89, 1.78)	0.193	1.26 (0.89, 1.78)	0.192

Supplementary Table ST7a: Predictors of progression to esophageal carcinoma after exclusion of estimated esophageal squamous cell cancers: Demographic and lifestyle factors

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CL)	P Value	HR (95% CL)	P Value
Age (per yr)	1.02 (1.01, 1.04)	0.001	1.04 (1.02, 1.05)	<0.0001
Male sex	2.32 (1.42, 3.81)	0.001	2.75 (1.63, 4.64)	<0.0001
Ever smoker	1.17 (0.78, 1.76)	0.456	1.03 (0.67, 1.59)	0.886
BMI (normal)	Reference			
Overweight (BMI 25-29.9)	1.72 (1.06, 2.81)	0.029	1.68 (1.04, 2.74)	0.036
Obese I (BMI 30-34.9)	1.47 (0.80, 2.69)	0.216	1.69 (0.89, 3.21)	0.109
Obese II (BMI > 34.9)	1.43 (0.19, 10.52)	0.725	2.50 (0.33, 18.79)	0.375
Hiatal Hernia	0.97 (0.58, 1.60)	0.899	0.96 (0.58, 1.59)	0.873
Diabetes	0.66 (0.21, 2.07)	0.472	0.76 (0.14, 3.96)	0.741

Supplementary Table ST7b: Conventional model: Predictors of progression to esophageal carcinoma after exclusion of estimated esophageal squamous cell cancers – Medications

Drugs	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
PPIs	0.89 (0.52, 1.55)	0.692	0.96 (0.54, 1.69)	0.879
NSAIDs	0.98 (0.65, 1.49)	0.933	0.98 (0.64, 1.49)	0.924
Statins	0.82 (0.47, 1.41)	0.469	0.67 (0.37, 1.21)	0.181
Metformin	0.45 (0.11, 1.84)	0.268	0.29 (0.05, 1.72)	0.174
Insulin	0.70 (0.10, 5.02)	0.725	0.85 (0.18, 3.96)	0.831
OAD	0.72 (0.27, 1.98)	0.53	1.96 (0.37, 10.26)	0.426

Supplementary Table ST7c: Time varying model: Predictors of progression to esophageal carcinoma after exclusion of estimated esophageal squamous cell cancers - Medications

Drugs	HR (95% CI)	P value
PPIs	0.44 (0.36, 0.53)	<0.0001
NSAIDs	0.17 (0.01, 1.98)	0.155
Statins	0.60 (0.43, 0.83)	0.002
Metformin	0.58 (0.28, 1.21)	0.146
OAD	1.27 (0.90, 1.80)	0.18