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Clinical and Endoscopic Characteristics Associated with Post-Endoscopy Upper Gastrointestinal Cancers: a Systematic Review and Meta-analysis

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SUPPLEMENTARY APPENDIX

Contents

Supplementary table 1. Search Strategy

Ovid MEDLINE(R) ALL (from 1946) and Embase (from 1974) were searched via OvidSP. The most recent database search was on 22 November 2021.

1. ((barret$ or columnar) adj1 (esophag$ or oesophag$ or metaplasia)).ab,hw,kw,ti.
2. ((columnar adj1 lined) and (esophag$ or oesophag$)).ab,hw,kw,ti.
3. Barrett Esophagus/
4. (esophagus or esophageal or oesophagus or oesophageal or gastric or stomach or duoden$ or upper gastrointestinal or UGI or UGIT).ab,hw,kw,ti.
5. or/1-4
6. (cancer or carcinoma or adenocarcinoma or neoplas$ or malignan$ or progression or progressor$).ab,hw,kw,ti.
7. Esophageal Neoplasms/di, ep, et, mo
8. Stomach Neoplasms/di, ep, et, mo
9. Duodenal Neoplasms/di, ep, et, mo
10. or/6-9
11. (miss$ or prevalen$ or false negative or prediagnosis or "prior gastroscopy" or "not detected" or undetected or "prior to diagnosis" or (penultimate endoscopy or post-endoscopy or PEEC or PEGC or POUGIC or "post OGD upper gastrointestinal cancer" or PEUGIC or "post EGD upper gastrointestinal cancer")).ab,hw,kw,ti.
12. (interval adj6 (cancer or carcinoma or adenocarcinoma or neoplas$ or malignan$)).ti.
13. Diagnostic Errors/
14. or/11-13
15. Endoscopy/ or Endoscopy, Gastrointestinal/ or Endoscopy, Digestive System/
16. (endoscop$ or gastroscopy or OGD or EGD or esophagogastroduod$ or oesophagogastroduod$ or surveillance).ab,hw,kw,ti.
17. 15 or 16
18. (observational or epidemiologic$ or case-control or patients or cohort$ or cross-section$ or retrospective or prospective$).ab,hw,kw,ti.
19. 5 and 10 and 14 and 17 and 18
20. (conference abstract or editorial or erratum or note or news).st,mp. or (case report or systematic review or review of the literature or expert review or meta-analysis or review article or case series or consensus).ti. or (letter or review).pt.
21. (bile duct or biliary or cholangiopancreatography or ERCP or submucosal dissection or perforation or gastrectomy or esophagectomy or oesophagectomy or pancreaticoduodenectomy or transplant$ or neoadjuvant or chemotherapy or stent$ or helicobacter or bleeding or pancreatic or bariatric or trial).ti.
22. 19 not 20 not 21
23. remove duplicates from 22

Supplementary table 2. Adapted Newcastle-Ottawa Quality Assessment Scale

Selection

1) Representativeness of the sample: (Maximum 2 star)

a) Truly representative of the average in the target population. ** (all subjects or random sampling of patients with upper GI cancer from general population or from endoscopy units).
b) Somewhat representative of the average in the target population. * (non-random sampling).
c) Selected group of users.
d) No description of the sampling strategy.

2) Non-respondents: (Maximum 1 star)

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is ≥ 70%. *
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.

3) PEUGIC Sample size (maximum 2 stars):

a) ≥ 400**
b) 100 – 399*
c) 50-99 0.5*
d) < 50

4) Ascertainment of the exposure (risk factor):

Score for exposure omitted, as not required.

5) Comparability:

Score for comparability omitted, as not required.

Post endoscopy upper gastrointestinal cancer definition

6) period excluded after first "cancer-negative" endoscopy (maximum 1 stars)

a) 12 months 0.5*
a) 6 months*
b) 3 months 0.5*
c) <3 months
d) 3 months if Barrett's cohort*

7) upper limit of diagnosis after first "cancer-negative" endoscopy (maximum 2 stars)

a) Within 3 years**
b) Within 2 years*
c) Within 1 year
d) Within 1 year if Barrett's cohort**

Outcome ascertainment

8) Outcome ascertainment: (Maximum 2 stars)

Assessment of the outcome.
a) Independent blind assessment. **
b) Record linkage (including endoscopy records). **
c) Self report. *
d) No description.

8) Statistical test:

Requirement for statistical test omitted as not required.

Supplementary table 3. Studies selected for full text review which did not meet eligibility

Study, year	Reason excluded
MEDLINE and Embase search	
Amin, 2002[1]	Inclusion criteria 3-4 not met
Hammad, 2019[2]	Inclusion criteria 2-4 not met
Parasa, 2018[3]	Inclusion criteria 2-4 not met
Tramontano, 2017[4]	Inclusion criteria 2-4 not met
Cook, 2016[5]	Inclusion criteria 2-4 not met
Visrodia, 2016[6]	Inclusion criteria 2-4 met, however larger sample from same population extracted instead[7].
Bae, 2015[8]	Inclusion criteria 2-4 not met
Bhat, 2015[9]	Inclusion criteria 2-4 not met
Khalil, 2014[10]	Inclusion criteria 3-4 not met
Corley, 2013[11]	Inclusion criteria 2-4 not met
Grant, 2013[12]	Inclusion criteria 2-4 not met
Nam, 2012[13]	Inclusion criteria 3-4 not met
Sung, 2011[14]	Inclusion criteria 2-4 not met
Lee, 2011[15]	Inclusion criteria 2-4 not met
Vradelis, 2011[16]	Inclusion criteria 3-4 not met
Rubenstein, 2008[17]	Inclusion criteria 2-4 not met
Munk, 2007[18]	Inclusion criteria 3-4 not met
Lassen, 2005[19]	Inclusion criteria 2-4 not met
Cooper, 2002[20]	Inclusion criteria 2-4 not met
Podolosky, 1988[21]	Inclusion criteria 2-4 not met; select cohort with benign looking gastric ulcers.
Abi Doumeth, 2021[22]	Inclusion criteria 3-4 not met
Lim, 2021[23]	Inclusion criteria 2-4 not met; gastric cancer not reported separately from low or high grade dysplasia
Kunzmann, 2021[24]	Inclusion criteria 2-4 not met
Verbeek, 2012[25]	Inclusion criteria 3-4 not met; and exclusion criteria 4 met.
Nguyen, 2021[26]	Inclusion criteria 3-4 not met
Holmberg, 2017[27]	Inclusion criteria 3-4 not met
Ren, 2013[28]	Inclusion criteria 2-4 not met
Vyberg, 1983[29]	Inclusion criteria 2-4 not met
Royston, 2016[30]	Inclusion criteria 3-4 not met
Wenker, 2018[31]	Inclusion criteria 2-4 not met
Holmberg, 2021[32]	Inclusion criteria 3-4 not met
Taninaga, 2019[33]	Inclusion criteria 2-4 not met
Park, 2015[34]	Inclusion criteria 3-4 not met
Stell, 2004[35]	Inclusion criteria 2-4 not met
Evans, 1985[36]	Inclusion criteria 2-4 not met
Voutilainen, 2005[37]	Inclusion criteria 2-3 not met
Bramble, 2000[38]	Inclusion criteria 2-3 not met
Hosokawa, 1998[39]	Inclusion criteria 1-3 met; however, overlapping population with more contemporaneous cohort[40].
Citation searching from two relevant systematic reviews[41, 42]	
De Jonge, 2010[43]	Inclusion criteria 3-4 not met
Bhat, 2011[44]	Inclusion criteria 3-4 not met
Hvid-Jensen, 2011[45]	Inclusion criteria 3-4 not met

Picardo, 2015[46]	Inclusion criteria 3-4 not met
Krishnamoorthi, 2017[47]	Inclusion criteria 3-4 not met
Nguyen, 2017[48]	Inclusion criteria 3-4 not met
Peters, 2019[49]	Inclusion criteria 3-4 not met
Kambhampati, 2020[50]	Inclusion criteria 3-4 not met
O'Byrne, 2020[51]	Inclusion criteria 2-4 not met

While the definition of PEEC/PEEN has only very recently been refined in the context of Barrett's surveillance or screening with a window of six to 36 months[52] (an interval also consistent with the World Endoscopy Organisation definition for PCCRC at three years for the purpose of benchmarking[53]), to ensure our review was comprehensive we did not exclude studies based on the time period excluded after a negative endoscopy, however reported this window for each study and incorporated the definition in the quality assessment.

Supplementary table 4. Meta-analysis of characteristics of post-endoscopy and initially detected gastric cancers stratified by population.

Factor	Unselected			Screening			$P_{interaction}$
	Studies / Estimates	Effect size (95% CI)	I^2	Studies Estimates	Effect size (95% CI)	I^2	
Demographic							
Age[a]	3/3	-1.70 (-4.83-1.43)	93.7%	2/2	1.16 (-1.98-4.30)	64.3%	0.207
Male	10/12	0.93 (0.74-1.16)	73.5%	3/3	1.01 (0.68-1.52)	34.8%	0.705
Endoscopic/procedural							
Experienced endoscopist	2/2	0.76 (0.32-1.81)	84.4%	1/1	1.14 (0.62-2.10)	-	0.454
H. Pylori	2/2	1.61 (0.91-2.85)	0.0%	1/1	0.57 (0.28-1.14)	-	0.023
Intestinal metaplasia	-	-	-	1/1	4.85 (1.86-12.69)		-
Tumour-related							
Stage 1 vs. 2-4	4/4	1.77 (1.31-2.39)	0.0%	2/2	3.44 (2.23-5.31)	4.0%	0.014
Stage 1-2 vs. 3-4	3/3	1.73 (1.33-2.25)	0.0%	1/1	4.36 (2.97-6.39)	-	<0.001
Stage 1-3 vs. 4	4/4	1.27 (0.97-1.67)	10.9%	1/1	5.28 (2.90-9.61)	-	<0.002
Proximal gastric cancer	9/9	0.92 (0.78-1.07)	7.8%	1/1	0.08 (0.00-1.36)	-	0.093
Medial gastric cancer	9/9	1.30 (1.01-1.68)	62.0%	1/1	1.16 (0.49-2.74)	0.0%	0.794
Distal gastric cancer	9/9	0.89 (0.74-1.07)	27.6%	1/1	2.10 (0.88-5.00)	-	0.058
Flat/depressed[b]	1/1	2.37 (1.41-3.97)	-	1/1	1.15 (0.50-2.62)	-	0.144

Abbreviations: CI, confidence interval.
[a]Effect size expressed as mean difference. All other effect sizes expressed as odds ratios
[b]Compared with sessile/mass

Supplementary table 5. Meta-analysis of characteristics of post-endoscopy and initially detected esophageal cancers stratified by population.

	Esophageal cancer (unselected cohorts)			BE-EAC (surveillance cohorts)			$P_{interaction}$
Factor	**Studies / Estimates**	**Odds ratio (95% CI)**	I^2	**Studies / Estimates**	**Odds ratio (95% CI)**	I^2	
Demographic							
Male	5/5	0.83 (0.64-1.07)	38.3%	1/1	0.37 (0.17-0.77)	-	0.042
Non white	1/1	5.67 (1.46-21.98)	-	1/1	0.70 (0.32-1.52)	-	0.009
Clinical							
Dysphagia	2/2	0.14 (0.10-0.20)	0.0%	1/1	0.35 (0.18-0.68)	-	0.020
Weight loss	2/2	0.72 (0.20-2.64)	64.1%	1/1	0.87 (0.38-1.99)	-	0.810
Anemia	2/2	1.34 (0.86-2.09)	0.0%	1/1	1.14 (0.57-2.29)	-	0.693
Reflux	2/2	2.69 (2.28-3.18)	0.0%	1/1	1.95 (0.99-3.85)	-	0.369
Tumour-related							
Stage 1 vs. 2-4	2/2	4.03 (0.62-26.30)	71.1%	1/1	6.22 (0.97-39.81)	-	0.747
Stage 1-2 vs. 3-4	2/2	3.41 (2.75-4.23)	0.0%	1/1	13.70 (0.72-260.74)	-	0.356
Stage 1-3 vs. 4	2/2	2.19 (1.70-2.83)	0.0%	1/1	6.35 (0.33-123.70)	-	0.484

Abbreviations: BE, Barrett's esophagus; CI, confidence interval; EAC, esophageal adenocarcinoma

Supplementary table 6. Meta-analysis of characteristics of post-endoscopy and initially detected upper gastrointestinal cancers in all cohorts stratified by time period used to define PEUGIC.

PEUGIC definition	< 12 months			< 24 months			< 36 months			$P_{interaction}$
Factor	**Studies / Estimates**	**Effect size (95% CI)**	I^2	**Studies / Estimates**	**Effect size (95% CI)**	I^2	**Studies / Estimates**	**Effect size (95% CI)**	I^2	
PEUGIC Prevalence[a]	5/5	9.2% (6.0%-13.0%)	79.2%	4/4	12.3% (7.4%-18.2%)	90.9%	16/16	10.8% (7.9%-14.1%)	99.1%	0.680
Demographic										
Age[b]	-	-	-	2/2	1.29 (-0.96-3.54)	50.9%	6/8	-0.61 (-2.12-0.90)	83.7%	0.168
Male	3/3	0.67 (0.28-1.59)	67.4%	3/3	1.11 (1.03-1.20)	0.0%	13/15	0.85 (0.74-0.98)	59.4%	0.003
Clinical										
Any alarm symptoms	1/1	2.46 (1.04-5.82)	-	-	-	-	4/5	0.34 (0.24-0.47)	58.9%	<0.001
Dysphagia	1/1	0.35 (0.18-0.68)	-	-	-	-	3/5	0.38 (0.16-0.73)	85.9%	0.867
Weight loss	1/1	0.87 (0.38-1.99)	-	-	-	-	2/4	0.50 (0.28-0.92)	20.9%	0.289
Anaemia	1/1	1.14 (0.57-2.29)	-	-	-	-	2/4	0.62 (0.23-1.64)	85.1%	0.317
Anorexia	-	-	-	-	-	-	1/2	0.62 (0.34-1.14)	0.0%	-
Vomiting	1/1	1.66 (0.67-4.12)	-	-	-	-	3/5	0.69 (0.36-1.30)	55.2%	0.120
Abdominal mass	-	-	-	-	-	-	1/2	1.03 (0.47-2.23)	0.0%	-
Haematemesis/malena	-	-	-	-	-	-	3/5	1.20 (0.75-1.91)	37.2%	-
Reflux	1/1	1.95 (0.99-3.85)	-	-	-	-	1/2	2.69 (2.28-3.18)	0.0%	0.369
PPI therapy	-	-	-	-	-	-	2/2	4.13 (2.47-6.88)	0.0%	-
Endoscopic/procedural										
High definition endoscope	-	-	-	-	-	-	2/2	0.78 (0.50-1.23)	0.0%	-
Sedation	-	-	-	-	-	-	1/1	0.44 (0.18-1.09)	-	-
Inpatient setting	-	-	-	-	-	-	2/3	0.86 (0.58-1.28)	65.0%	-
Experienced endoscopist	1/1	1.07 (0.47-2.45)	-	1/1	1.14 (0.62-2.10)	-	3/3	1.34 (0.39-4.61)	93.0%	0.955
Gastroenterologist	-	-	-	-	-	-	2/2	0.63 (0.29-1.38)	58.3%	-
Tumour-related										
Stage 1 vs. 2-4	1/1	6.22 (0.97-39.81)	-	1/1	9.69 (1.24-75.62)	-	6/6	2.53 (1.38-4.64)	88.6%	0.342
Stage 1-2 vs. 3-4	1/1	13.70 (0.72-260.74)	-	-	-	-	6/6	2.51 (1.72-3.66)	79.2%	0.262
Stage 1-3 vs. 4	1/1	6.35 (0.33-123.70)	-	1/1	6.37 (0.37-109.46)	-	9/9	1.45 (0.91-2.32)	91.8%	0.390
Upper esophagus	-	-	-	1/1	2.57 (0.57-11.63)	-	5/5	1.35 (1.03-1.76)	0.0%	0.407
Mid esophagus	-	-	-	1/1	1.88 (0.43-8.26)	-	5/5	0.84 (0.39-1.78)	88.6%	0.340
Lower esophagus	-	-	-	1/1	0.33 (0.08-1.27)	-	5/5	0.99 (0.77-1.27)	24.4%	0.117
Gastroesophageal junction	-	-	-	-	-	-	2/2	0.77 (0.64-0.94)	0.0%	-
EAC vs. ESCC	-	-	-	1/1	0.76 (0.20-2.85)	-	4/4	1.16 (0.87-1.54)	44.9%	0.539
Proximal gastric cancer	1/1	0.08 (0.00-1.36)	-	-	-	-	9/9	0.92 (0.74-1.07)	7.8%	0.093
Medial gastric cancer	1/1	1.16 (0.49-2.74)	-	-	-	-	9/9	1.30 (1.01-1.68)	62.0%	0.794
Distal gastric cancer	1/1	2.10 (0.88-5.00)	-	-	-	-	9/9	0.89 (0.74-1.07)	27.6%	0.058
Flat/depressed[c]	1/1	1.15 (0.50-2.62)	-	-	-	-	1/1	2.37 (1.41-3.97)	-	0.144

Abbreviations: CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; PEUGIC, post-endoscopy upper gastrointestinal cancer; PPI, Proton pump inhibitor; SCC, squamous cell carcinoma.

[a]Prevalence expressed as the proportion of PEUGIC diagnosed from all upper gastrointestinal cancers (initially detected + PEUGIC)
[b]Effect size expressed as mean difference. All other effect sizes expressed as odds ratios
[c]compared with sessile/mass
< 12, <24 and <36 month groups were mutually exclusive for the purpose of analyses (for example, the single study defined in the < 12 month group did not also appear in the < 24 month group).

Supplementary table 7. Meta-analysis of characteristics of post-endoscopy and initially detected upper gastrointestinal cancers stratified by time period excluded after the initial "cancer-negative" endoscopy to define PEUGIC.

PEUGIC definition	Excludes ≥ 6 months			Excludes ≤ 6 months			$P_{interaction}$
Factor	**Studies / Estimates**	**Effect size (95% CI)**	I^2	**Studies / Estimates**	**Effect size (95% CI)**	I^2	
PEUGIC prevalence[a]	5/5	16.5% (9.1%-25.6%)	99.8%	20/20	9.3% (7.6%-11.3%)	92.7%	0.080
Demographic							
Age[b]	4/5	-0.76 (-2.49-0.98)	95.2%	4/5	0.98 (-0.93-2.88)	20.5%	0.187
Male	5/6	0.87 (0.70-1.08)	90.5%	14/15	0.87 (0.69-1.09)	55.3%	0.975
Clinical							
Any alarm symptoms	1/2	0.25 (0.19-0.33)	85.4%	4/4	0.66 (0.23-1.89)	84.0%	0.245
Dysphagia	1/2	0.26 (0.07-0.96)	94.3%	3/4	0.47 (0.19-0.73)	43.0%	0.427
Weight loss	1/2	0.41 (0.23-0.73)	0.0%	2/3	0.89 (0.45-1.77)	5.1%	0.090
Anemia	1/2	0.66 (0.14-3.13)	94.5%	2/3	0.84 (0.42-1.69)	33.9%	0.780
Anorexia	1/2	0.62 (0.34-1.14)	0.0%	-	-	-	-
Vomiting	1/2	0.43 (0.28-0.65)	0.0%	3/4	1.39 (0.80-2.43)	0.0%	0.001
Abdominal mass	1/2	1.03 (0.47-2.23)	0.0%	-	-	-	-
Hematemesis/melena	1/2	1.06 (0.46-2.42)	77.3%	2/3	1.59 (0.82-3.05)	0.0%	0.450
Reflux	1/2	2.69 (2.28-3.18)	0.0%	1/1	1.95 (0.99-3.85)	-	0.369
PPI therapy	-	-	-	2/2	4.13 (2.47-6.88)	0.0%	-
Endoscopic/procedural							
High definition endoscope	-	-	-	2/2	0.78 (0.50-1.23)	0.0%	-
Inpatient setting	-	-	-	3/3	0.87 (0.60-1.26)	61.0%	-
Experienced endoscopist	-	-	-	5/5	1.21 (0.60-2.45)	84.4%	-
Tumour-related							
Stage 1 vs. 2-4	2/2	2.79 (1.75-4.44)	41.8%	7/7	2.99 (1.31-6.83)	87.8%	0.884
Stage 1-2 vs. 3-4	2/2	2.87 (1.21-6.81)	84.6%	5/5	2.42 (1.49-3.94)	77.1%	0.735
Stage 1-3 vs. 4	3/3	1.90 (0.60-6.04)	95.5%	8/8	1.42 (0.96-2.09)	56.2%	0.637
Upper esophagus	1/1	1.15 (0.72-1.82)	-	5/5	1.49 (1.08-2.06)	0.0%	0.360
Mid esophagus	1/1	1.09 (0.76-1.57)	-	5/5	0.89 (0.38-2.07)	76.8%	0.659
Lower esophagus	1/1	0.84 (0.58-1.22)	-	5/5	0.83 (0.52-1.35)	37.4%	0.990
Gastroesophageal junction	-	-	-	2/2	0.77 (0.64-0.94)	0.0%	-
EAC vs. ESCC	1/1	1.46 (1.12-1.91)	-	4/4	0.98 (0.80-1.20)	0.0%	0.019
Proximal gastric	3/3	0.88 (0.71-1.08)	13.5%	7/7	0.93 (0.65-1.33)	32.2%	0.767
Medial gastric	3/3	1.19 (0.58-2.41)	81.1%	7/7	1.30 (0.97-1.72)	42.5%	0.820
Distal gastric	3/3	0.97 (0.72-1.30)	30.0%	7/7	0.88 (0.65-1.20)	46.7%	0.655
Flat/sessile[c]	-	-	-	2/2	1.78 (0.88-3.57)	53.2%	-

Abbreviations: CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; PPI, Proton pump inhibitor; SCC, squamous cell carcinoma.

[a]Prevalence expressed as the proportion of PEUGIC diagnosed from all upper gastrointestinal cancers (initially detected + PEUGIC)

[b]Effect size expressed as mean difference. All other effect sizes expressed as odds ratios

[c]compared with sessile/mass

Supplementary table 8. Study-level risk of bias

First author, year	Representativeness	Non-respondents	Sample size	PEUGIC definition		Outcome	Total	Quality
				Period excluded	Upper limit			
Beck, 2021	2	1	0.5	1	2	2	8.5	H
Januszewicz, 2021	2	1	2	1	2	2	10	H
Vajravelu, 2021	2	1	0.5	0	2	2	7.5	H
Dhaliwal, 2020	2	1	0	0	2	2	7	H
Gavric, 2020	2	1	0	0	2	2	7	H
Januszewicz, 2019	2	1	0	0	2	2	7	H
Delgado Guillena, 2019	2	1	0	0	2	2	7	H
Hernanz, 2019	2	1	0.5	0	2	2	7.5	H
Tai, 2019	2	1	0	0	2	2	7	H
van Putten, 2018	2	1	0	1	2	2	8	H
Rodríguez de Santiago, 2018	2	1	0	0	2	2	7	H
Leung, 2018	2	1	2	1	1	2	9	H
Iida, 2018	1	0	0	0	1	2	4	L
Jin, 2018	2	0	2	0.5	2	2	8.5	H
Wang, 2016	2	1	0.5	1	2	2	8.5	H
Cheung, 2016	2	1	2	0.5	2	2	9.5	H
Hamashima, 2015	2	1	0	0	0	2	5	M
Chadwick, 2015	2	1	1	0.5	2	2	8.5	H
Cho, 2015	2	1	0.5	0	1	2	6.5	M
Chadwick, 2014	2	1	2	0.5	2	2	9.5	H
Raftopoulos, 2010	2	1	0.5	0	0	2	5.5	M
Hosokawa, 2007	2	1	1	0	2	2	8	H
Bloomfield, 2005	2	1	0	0	2	2	7	H
Yalamarthi, 2004	2	1	0	0	2	2	7	H
Hosokawa, 2001	2	1	0	0	2	2	7	H

Abbreviations: H, high quality; M, moderate quality; L, low quality; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary table 9. Multivariable meta-regression of recruitment years and (i) prevalence of PEUGIC, and (ii) in comparisons of PEUGIC vs. detected cancer: age at diagnosis, male sex and stage 1-3 vs. 4

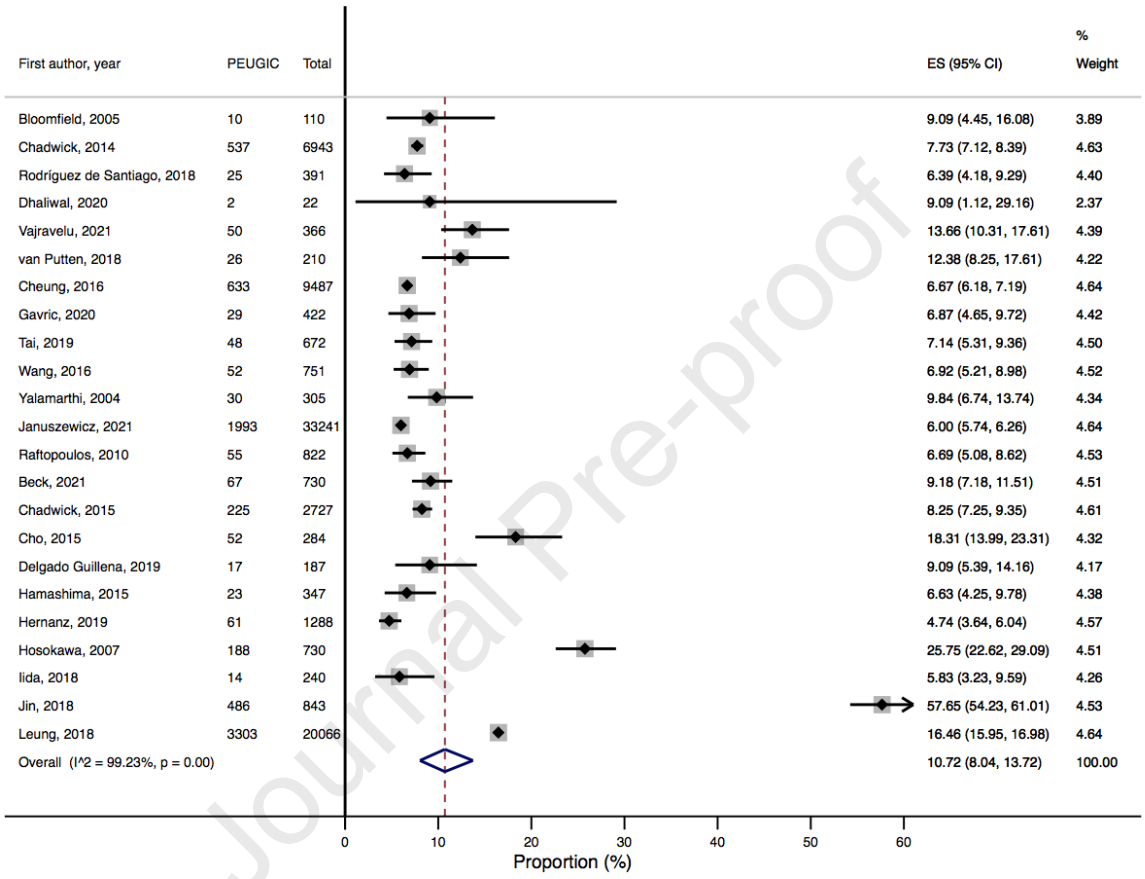
		Earliest recruitment year		Last recruitment year	
	Studies	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value
PEUGIC prevalence[a]	**25**	0.4% (-0.2%-1.0%)	0.223	-0.9% (-1.6%--0.2%)	0.011
Age at diagnosis[b]	**10**	0.16 (-1.73-2.04)	0.871	-0.05 (-2.30-2.20)	0.966
Male sex[c]	**21**	0.99 (0.94-1.03)	0.575	0.98 (0.92-1.05)	0.609
Stage 1-3 vs. 4[c]	**11**	0.91 (0.75-1.12)	0.378	0.89 (0.73-1.08)	0.226

Abbreviations: CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; PEUGIC, post-endoscopy upper gastrointestinal cancer;
[a]Risk difference per year
[b]Mean difference per year
[c]Odds ratio per year

During the time periods over which patients in individual studies were recruited, endoscope technology has dramatically improved. Early populations included patients examined with fiberscopes[54], and in addition modern video endoscopes have improved over time in terms of resolution. Although our systematic review did not demonstrate an association betwen high-resolution endoscope use and PEUGIC vs. detected cancers, this analysis was limited to two relatively small studies. We are therefore unable to exclude the plausible relationship between endoscope resolution and PEUGIC rates at a population level. It is also not clear whether endoscope technology could influence the effect sizes for individual characteristics in PEUGIC/detected cancer comparisons. To indirectly assess these points we undertook a post-hoc analysis to establish whether the earliest and last year of participant recruitment in each study was independently associated with (i) prevalence of PEUGIC in the studied population; (ii) the mean difference in age at diagnosis between PEUGIC and detected cancers; (iii) the sex distribution of PEUGIC vs. detected cancers; and (iv) cancer staging of PEUGIC vs. detected cancers (for stage I to III vs. IV). The latter three factors were selected as they were the comparisons with the highest numbers of contributing studies. We conducted multivariable metaregression, indication for the EGD (unselected cohort, screening and Barrett's esophagus surveillance), maximum duration of the exposure window for PEUGIC applied in individual studies (for example a window between 6-36 months was considered as a 30 month window) and the time interval after a cancer-negative EGD used to define PEUGIC and the cancer(s) studied (esophageal, gastric or a combination of upper gastrointestinal cancers).

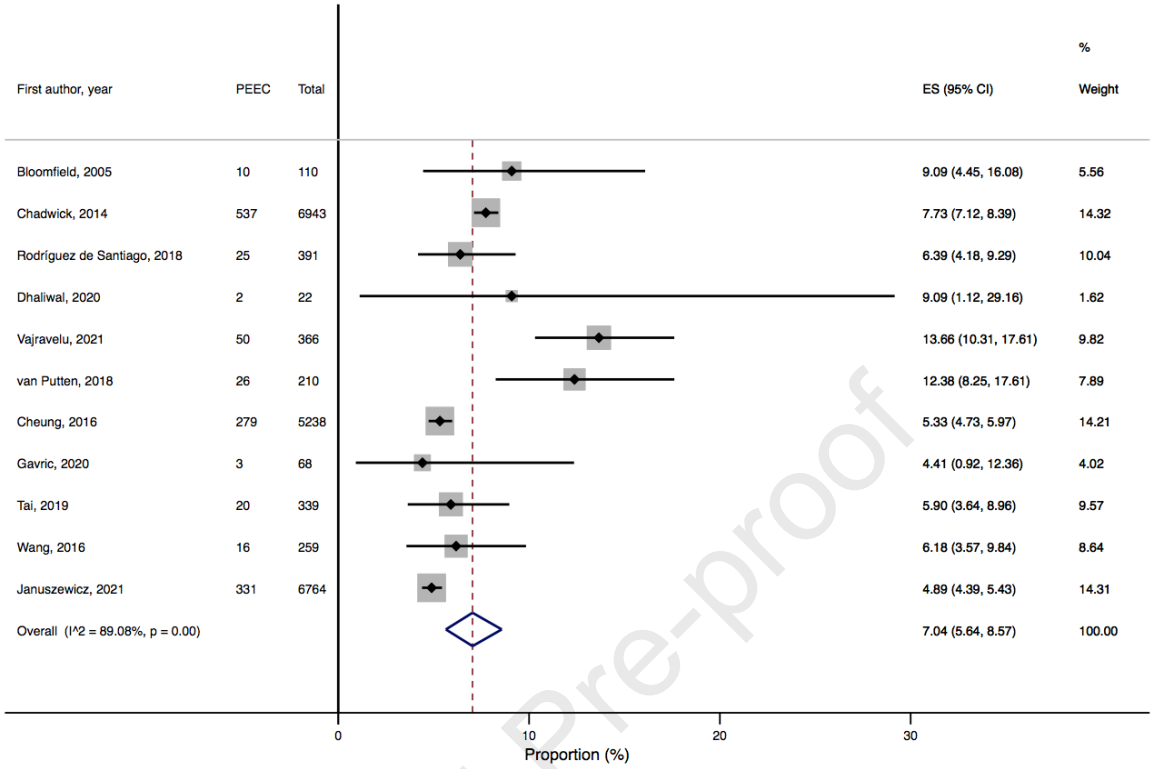
Earliest recruitment year was not associated with POUGIC proportions across studies, however last recruitment year was inversely associated with PEUGIC proportions. There were no other associations demonstrated at a study level with age at diagnosis, male sex or cancer stage at diagnosis.

Supplementary figure 1. Random-effects meta-analysis of proportions of post-endoscopy upper gastrointestinal cancer



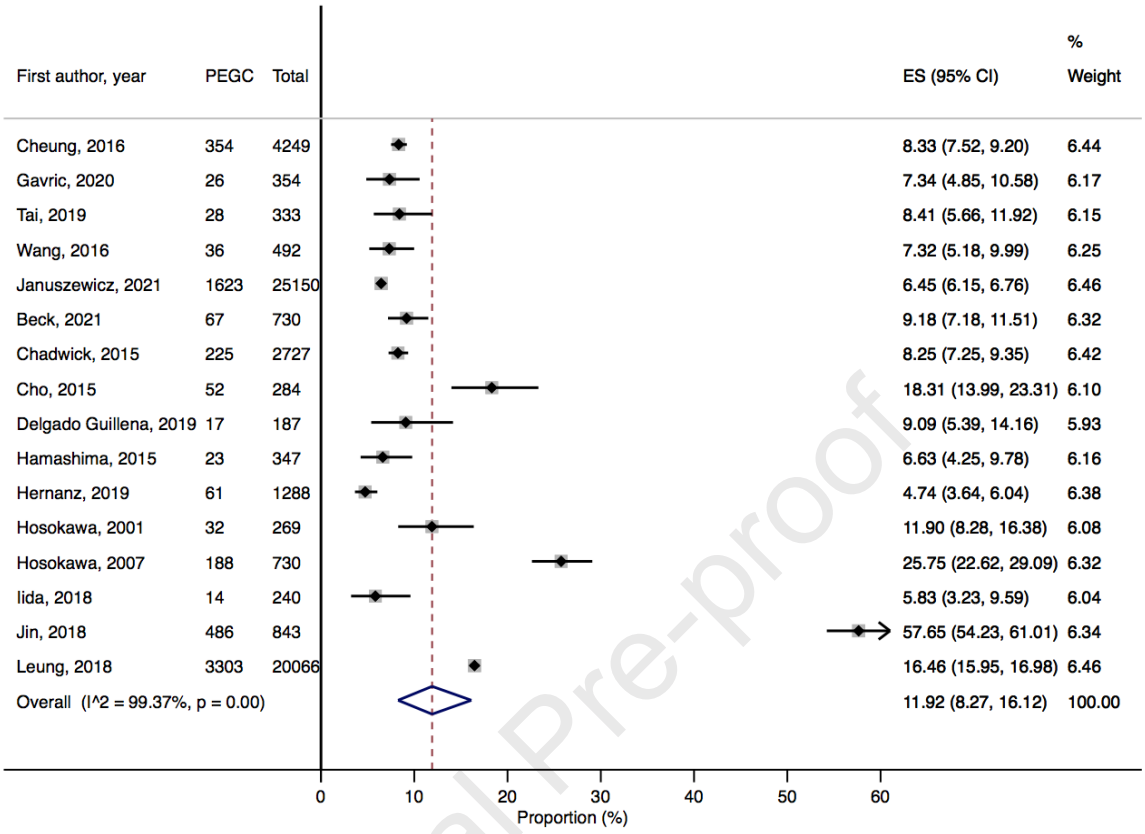
Abbreviations: PEUGIC, post-endoscopy upper gastrointestinal cancer
Note excluded smaller populations with potentially overlapping cases to prevent double counting[54, 55].

Supplementary figure 2. Random-effects meta-analysis of proportions of post-endoscopy esophageal cancer



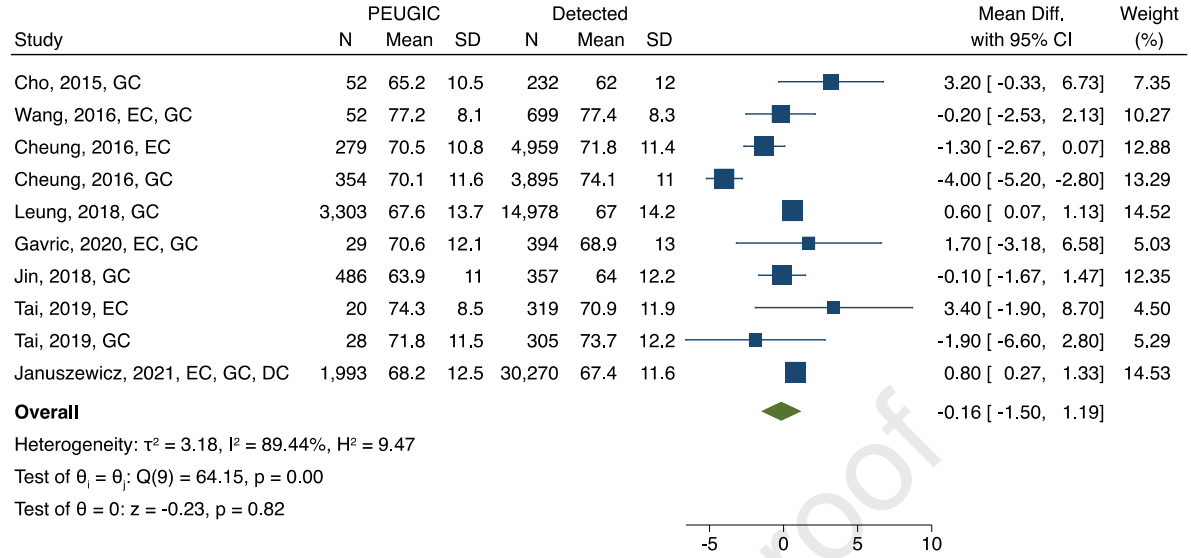
Abbreviations: PEEC, post-endoscopy esophageal cancer

Supplementary figure 3. Random-effects meta-analysis of proportions of post-endoscopy gastric cancer



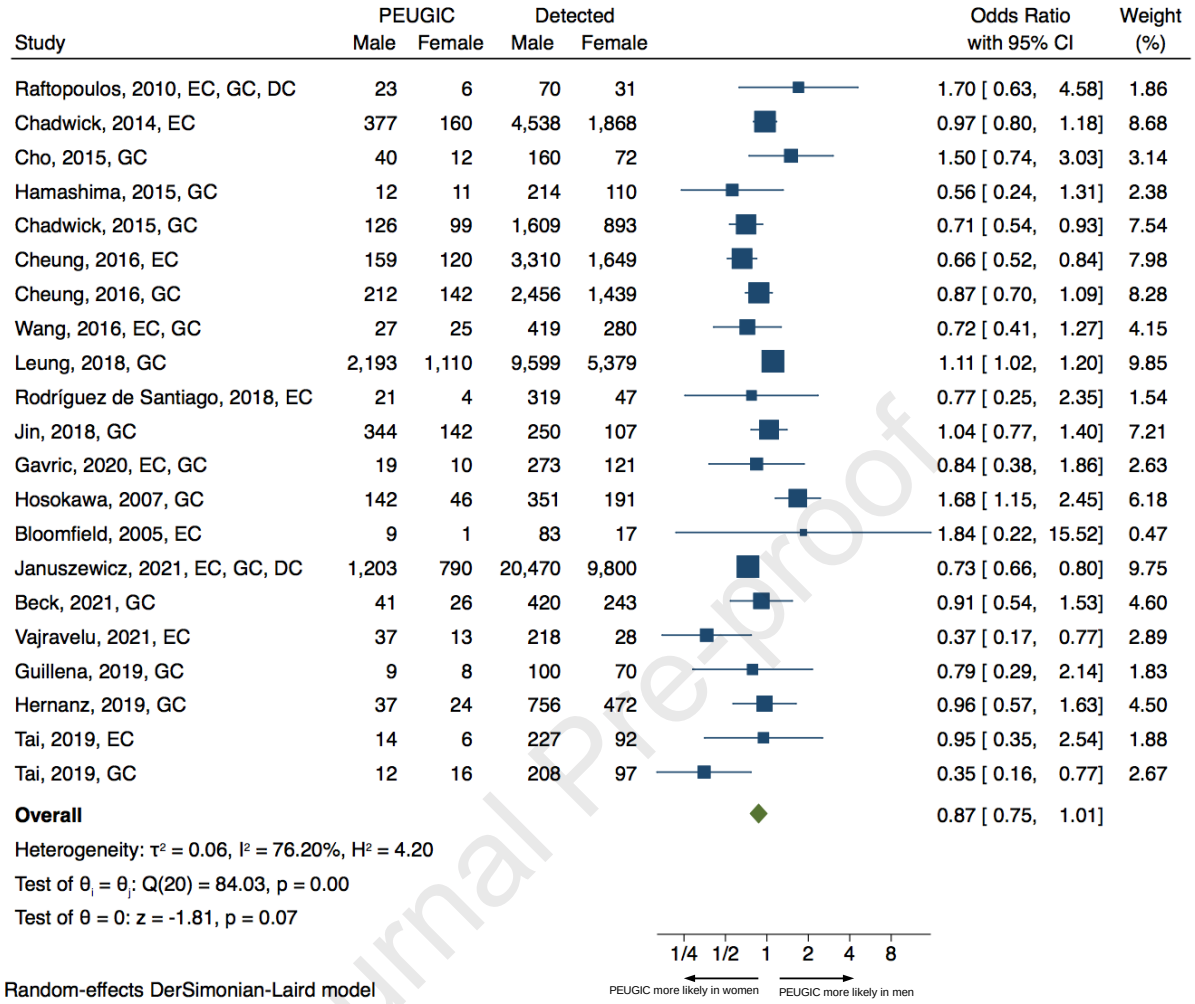
Abbreviations: PEGC, post-endoscopy gastric cancer

Supplementary figure 4. Mean difference in age (years) at diagnosis between PEUGIC and detected upper gastrointestinal cancers



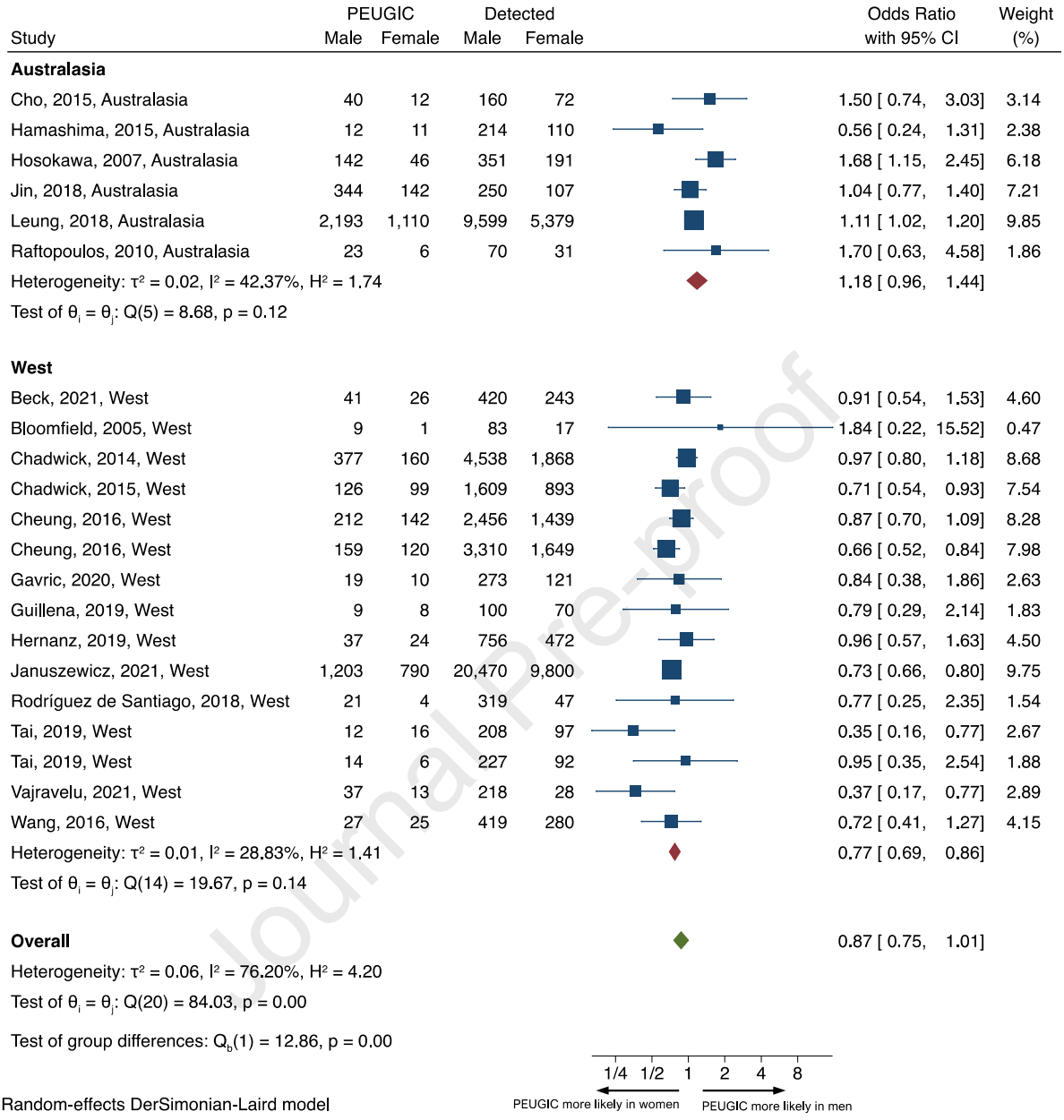
Abbreviations: DC, duodenal cancer; EC, esophageal cancer; GC, gastric cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 5. Comparison of sex between PEUGIC and detected upper gastrointestinal cancers



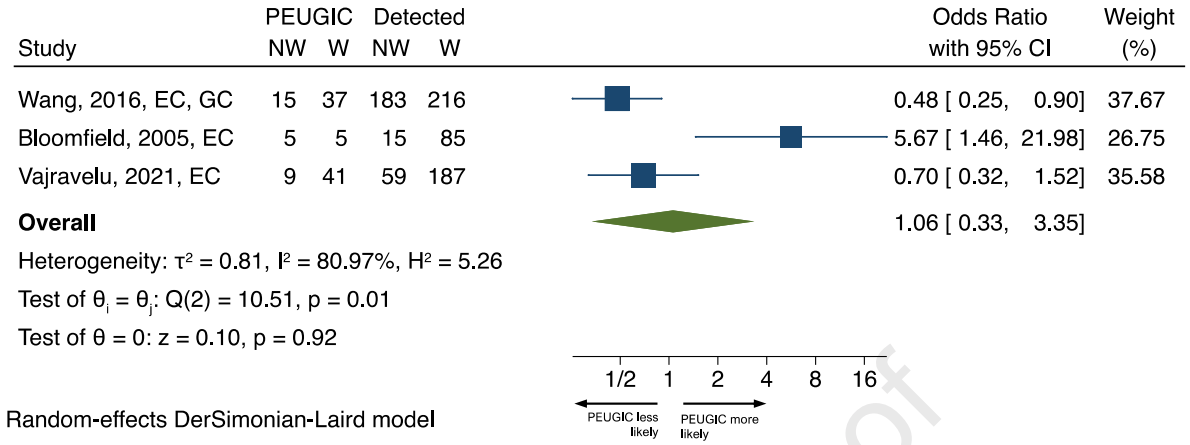
Abbreviations: DC, duodenal cancer; EC, esophageal cancer; GC, gastric cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 6. Comparison of sex between PEUGIC and detected upper gastrointestinal cancers stratified by geographic location (West vs. Australasia)



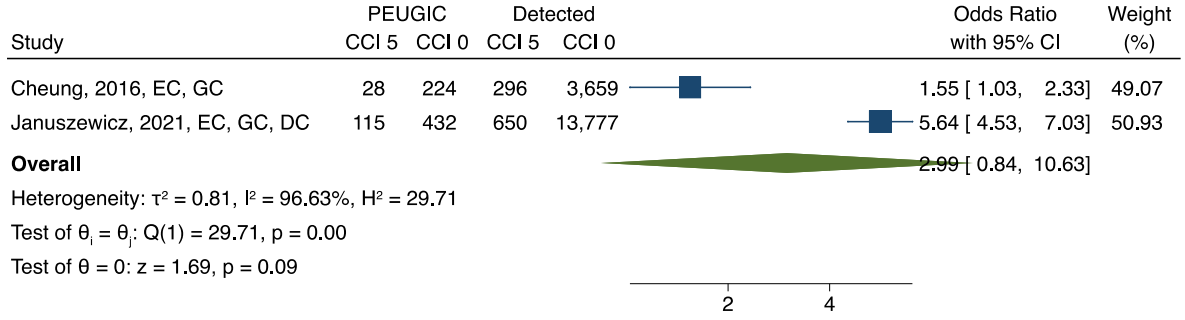
Abbreviations: PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 7. Comparison of ethnicity between PEUGIC and detected upper gastrointestinal cancers



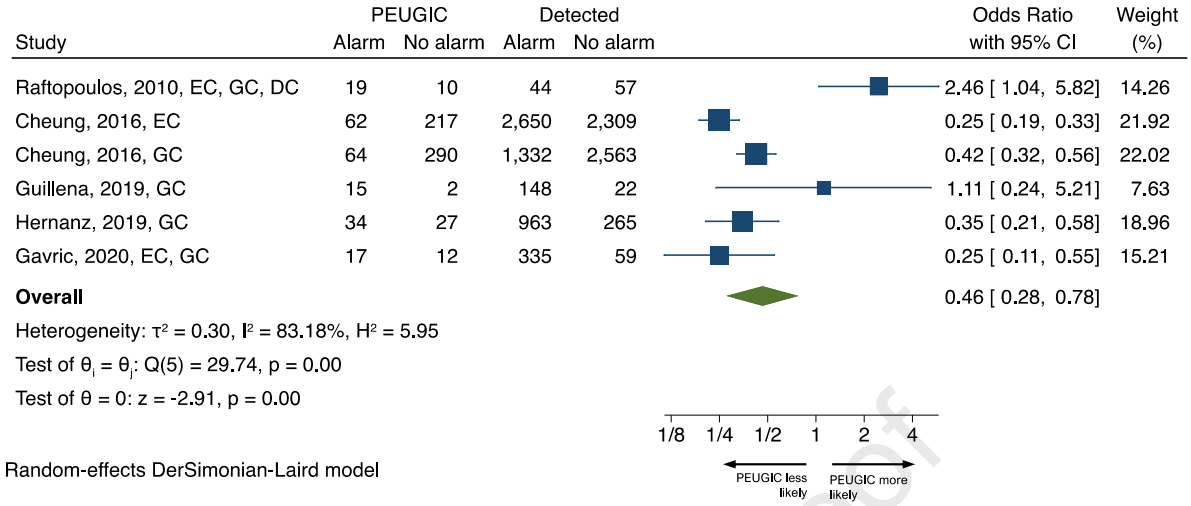
Abbreviations: EC, esophageal cancer; GC, gastric cancer; NW, non white; PEUGIC, post-endoscopy upper gastrointestinal cancer; W, White

Supplementary figure 8. Comparison of Charlson Comorbidity Index between PEUGIC and detected upper gastrointestinal cancers



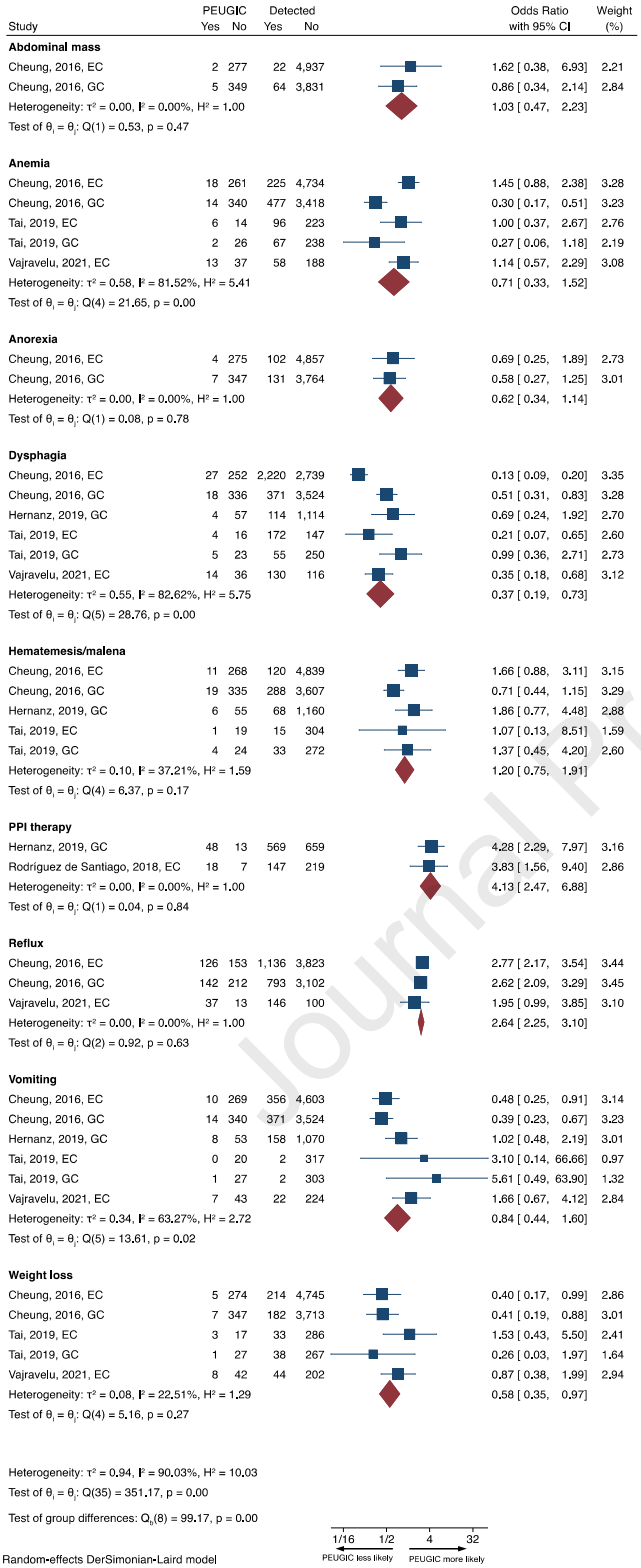
Abbreviations: CCI, Charlson Comorbidity Index; EC, esophageal cancer; GC, gastric cancer; NW, non white; PEUGIC, post-endoscopy upper gastrointestinal cancer; W, White Charlson comorbidity score (each co-morbidity assigned a weight from 1 – 6).

Supplementary figure 9. Comparison of alarm symptoms between between PEUGIC and detected upper gastrointestinal cancers



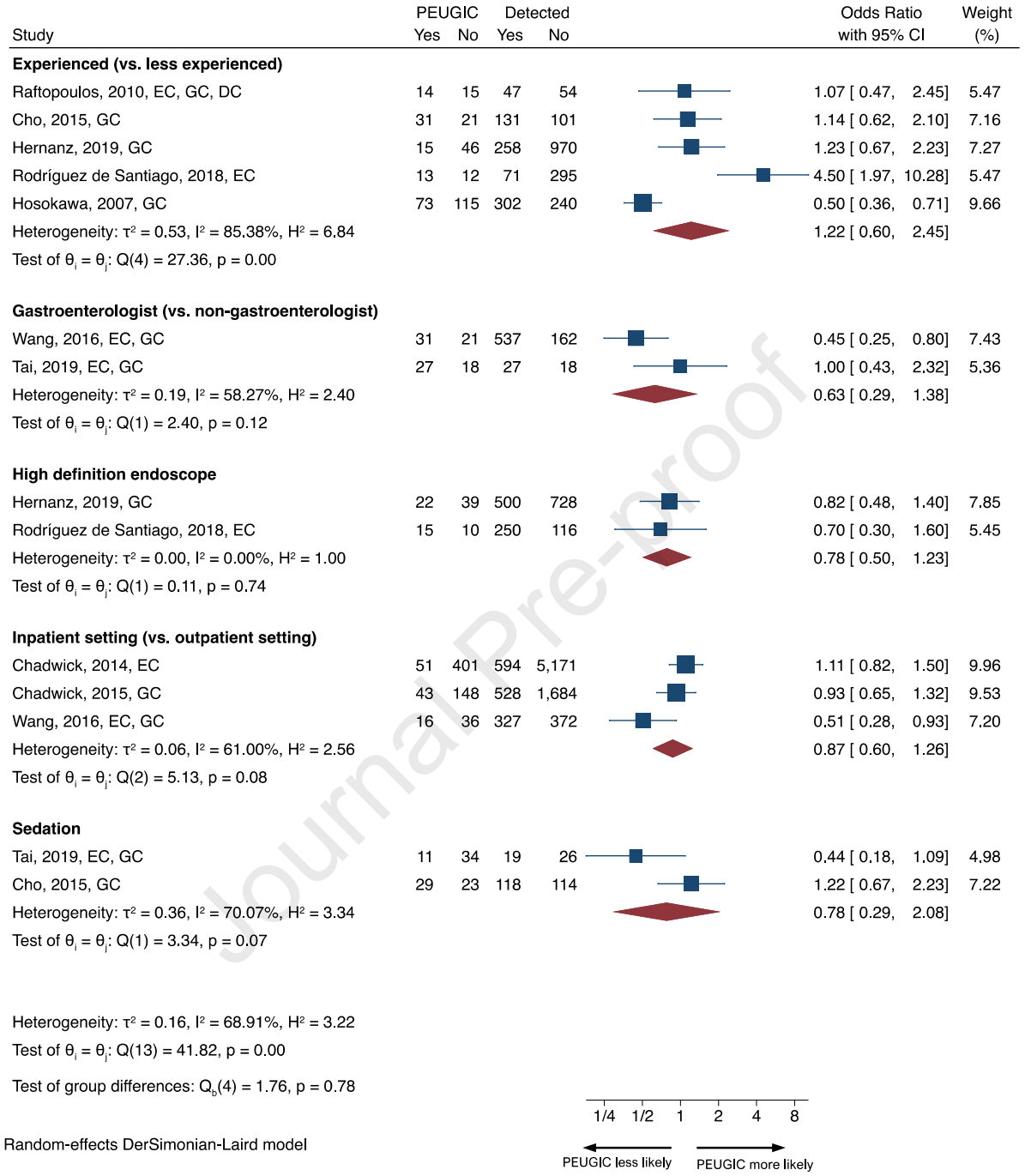
Abbreviations: DC, duodenal cancer; EC, esophageal cancer; GC, gastric cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 10. Comparison of alarm symptoms between PEUGIC and detected upper gastrointestinal cancers



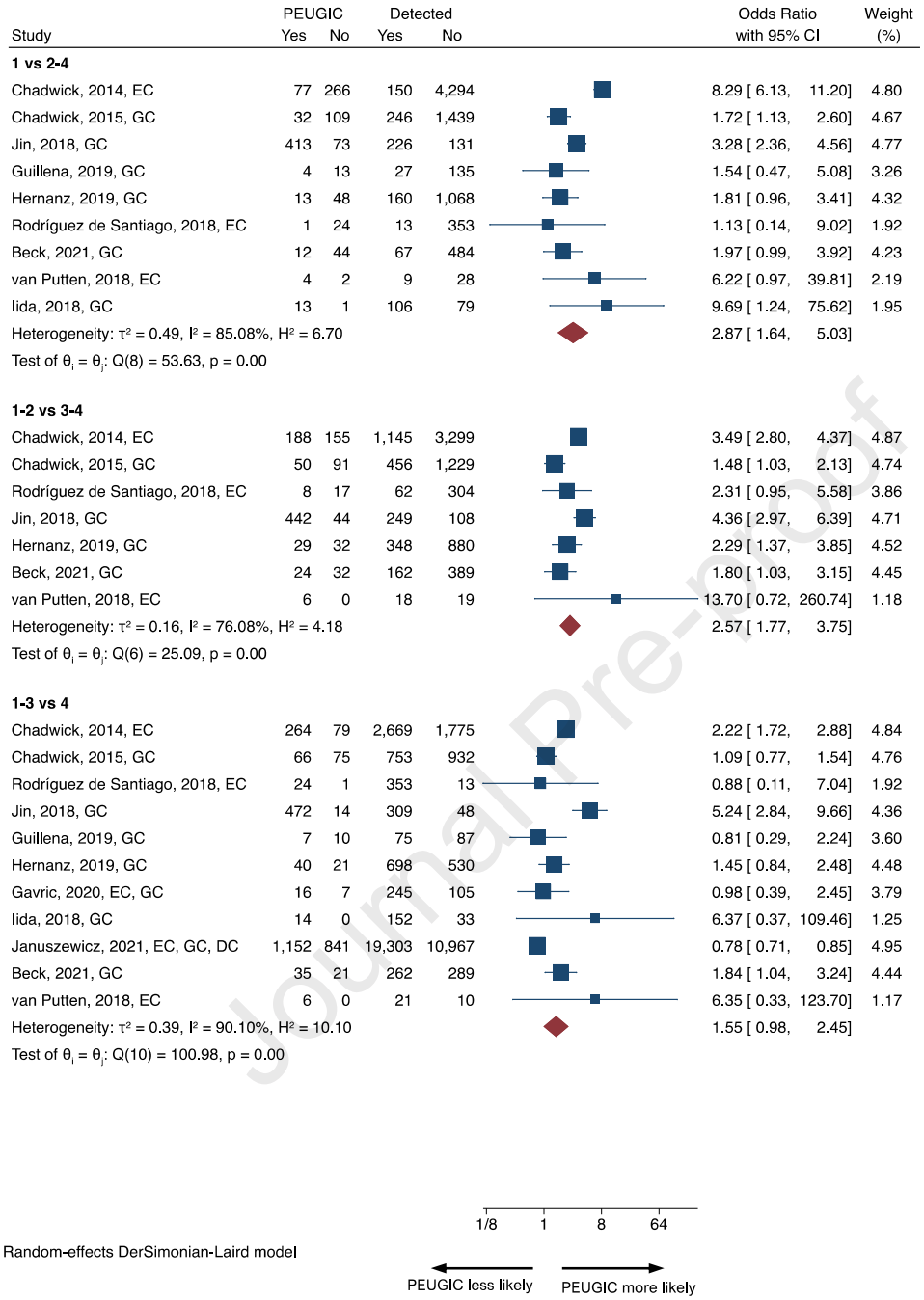
Abbreviations: DC, duodenal cancer; EC, esophageal cancer; GC, gastric cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 11. Comparison of endoscopic/procedural characteristics between PEUGIC and detected upper gastrointestinal cancers



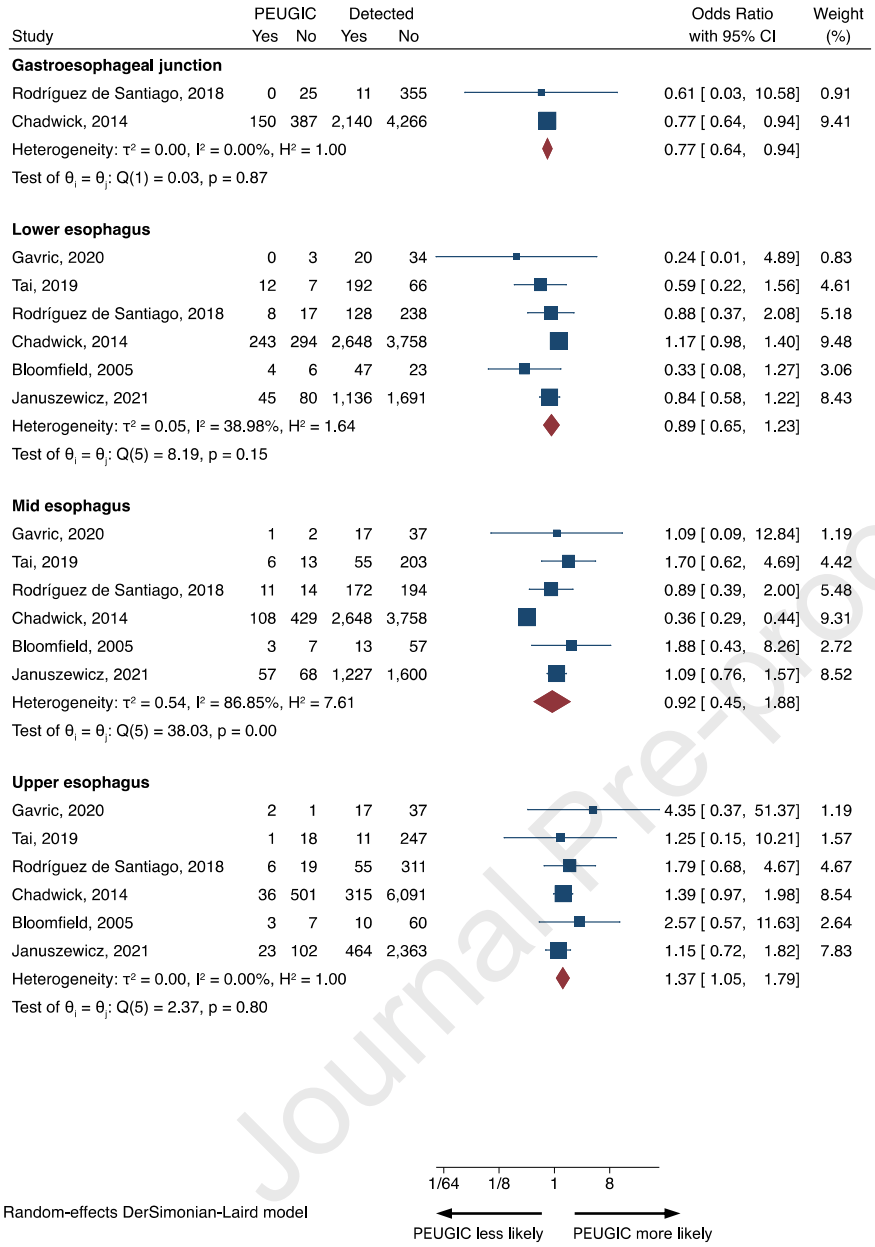
Abbreviations: DC, duodenal cancer; EC, esophageal cancer; GC, gastric cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 12. Comparison of tumor stage at diagnosis between PEUGIC and detected upper gastrointestinal cancers



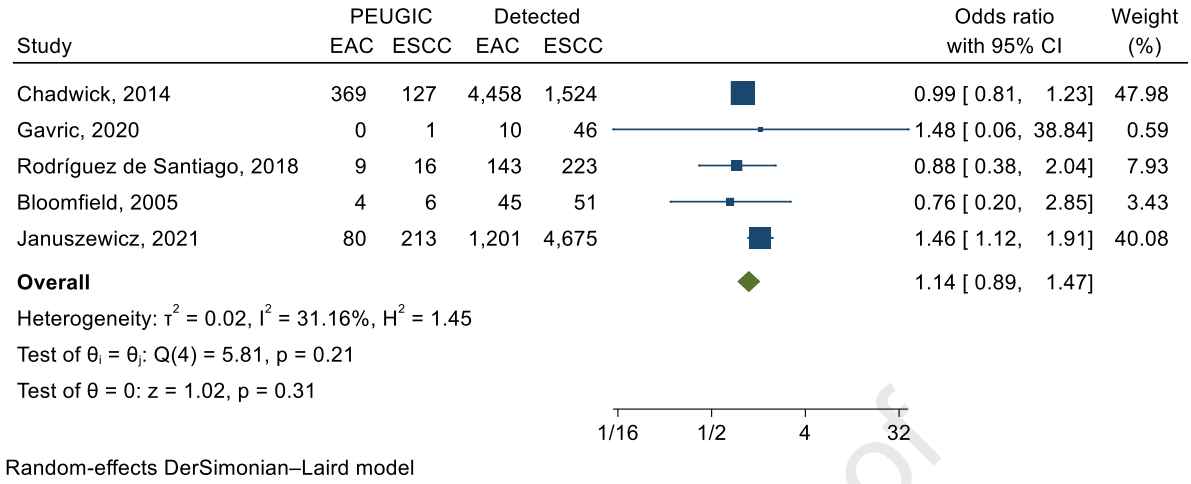
Abbreviations: DC, duodenal cancer; EC, esophageal cancer; GC, gastric cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer

Supplementary figure 13. Comparison of tumor site between PEUGIC and detected upper gastrointestinal cancers



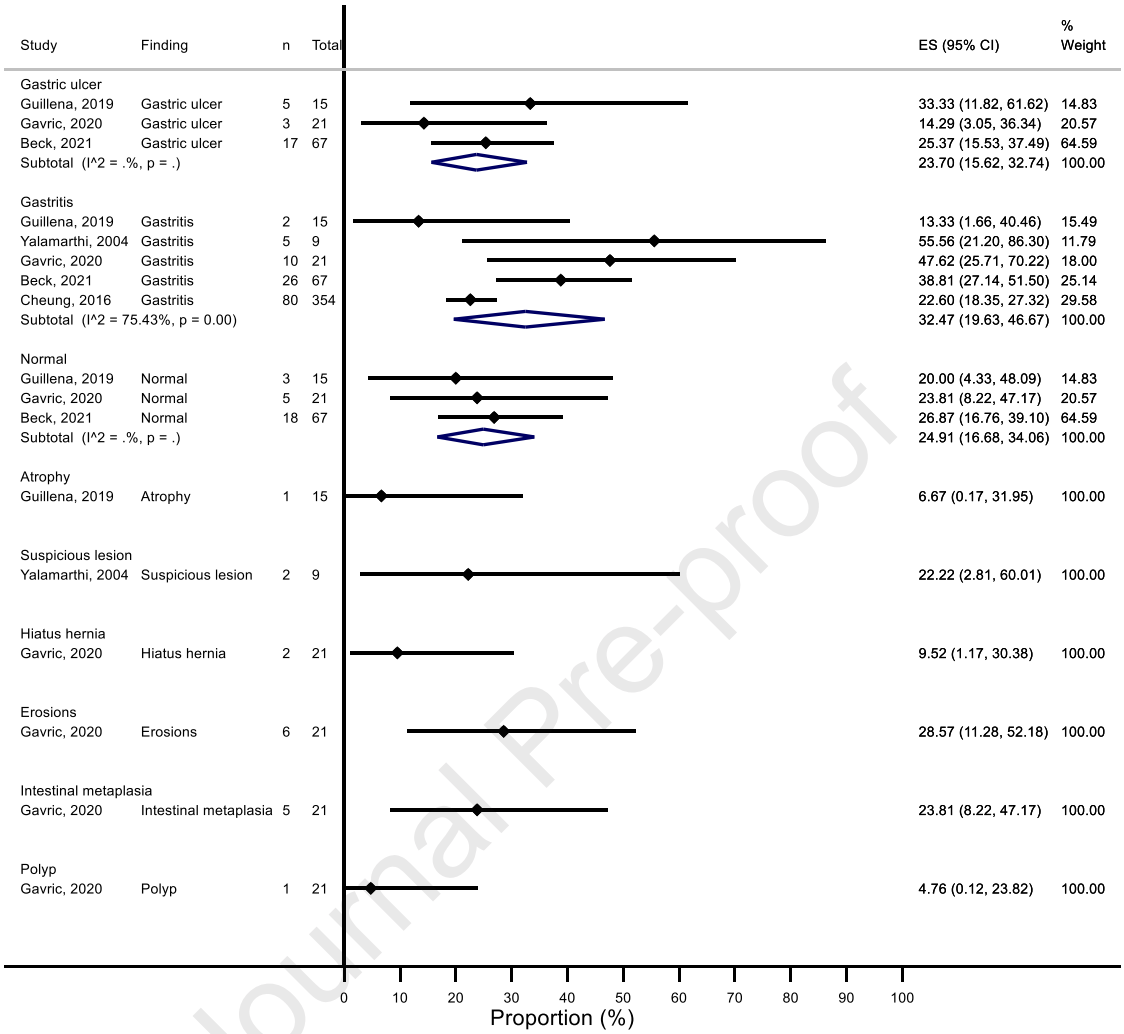
Abbreviations: PEUGIC, post-endoscopy upper gastrointestinal cancer
Comparisons: Gastroesophageal junction vs. lower + mid + upper esophagus; Lower vs. gastroesophageal junction + mid + upper esophagus; Mid esophagus vs. gastroesophageal junction + lower + upper esophagus; Upper esophagus vs. gastroesophageal junction + lower + mid esophagus

Supplementary figure 14. Comparison of histology between post-endoscopy and detected esophageal cancers



Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; PEUGIC, post-endoscopy upper gastrointestinal cancer.

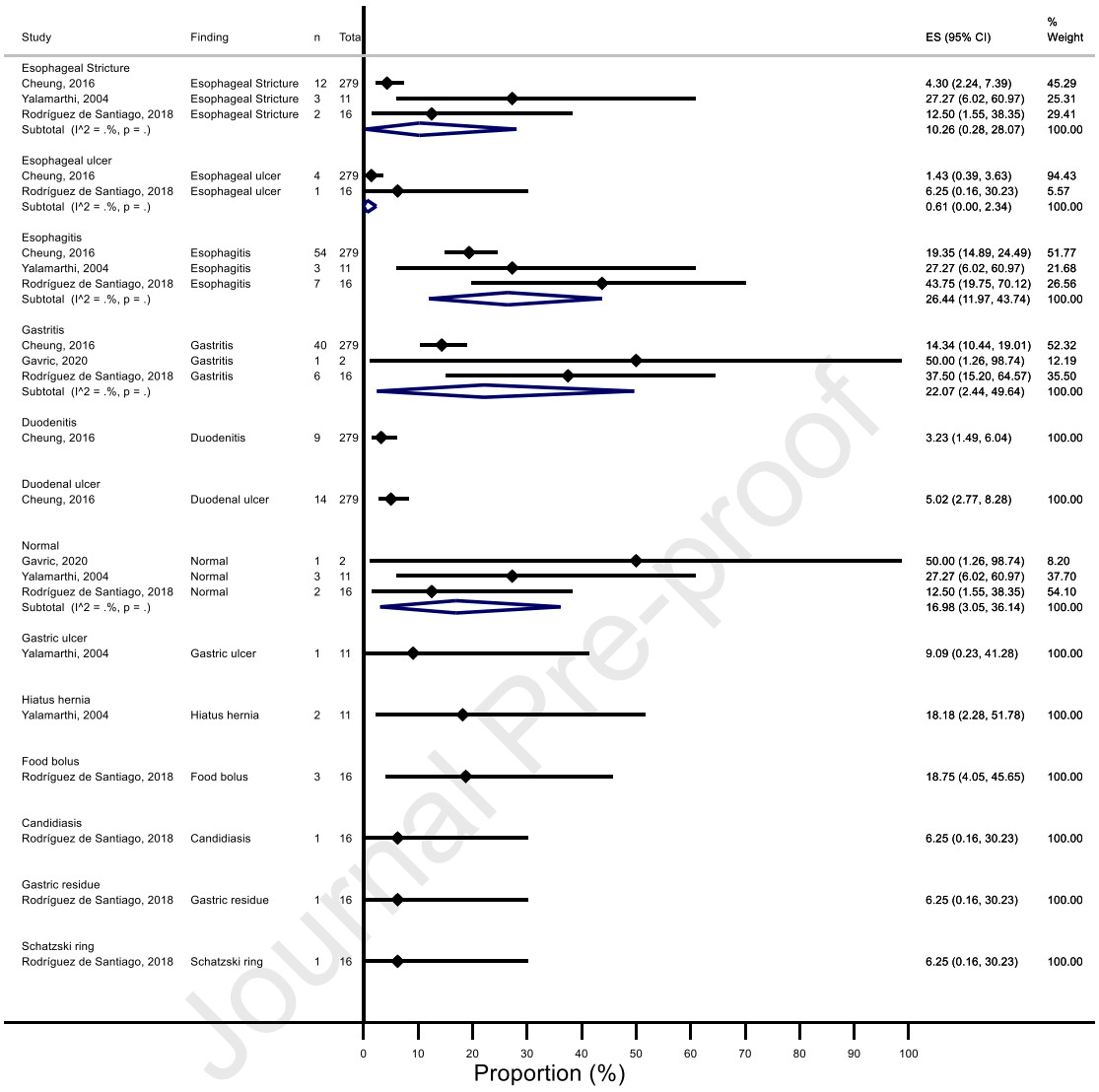
Supplementary figure 15. Meta-analysis of proportions of findings in the "cancer-negative" esophagogastroduodenoscopy preceding diagnosis of post-endoscopy gastric cancer.



Abbreviations: CI, confidence interval; n, number

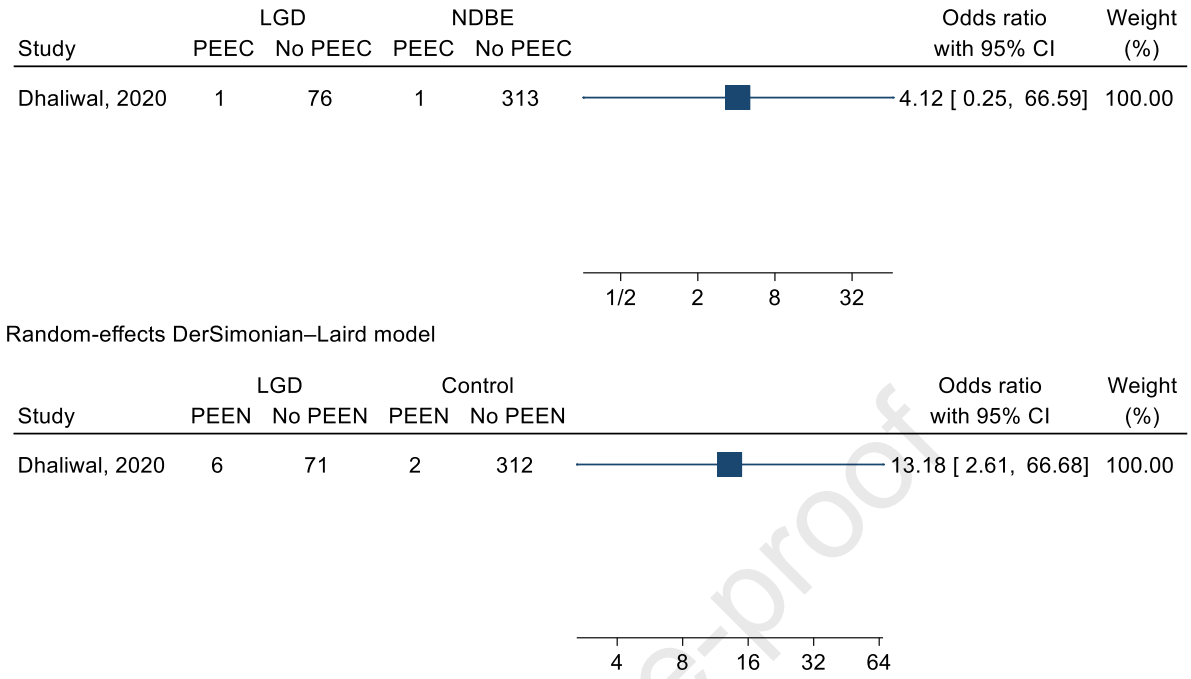
Abbreviations: n, number; PEUGIC, post-endoscopy upper gastrointestinal cancer. Endoscopic findings reported for PEUGIC diagnosed 6-36 months after a "cancer-negative" endoscopy.

Supplementary figure 16. Meta-analysis of proportions of findings in the "cancer-negative" esophagogastroduodenoscopy preceding diagnosis of post-endoscopy esophageal cancer



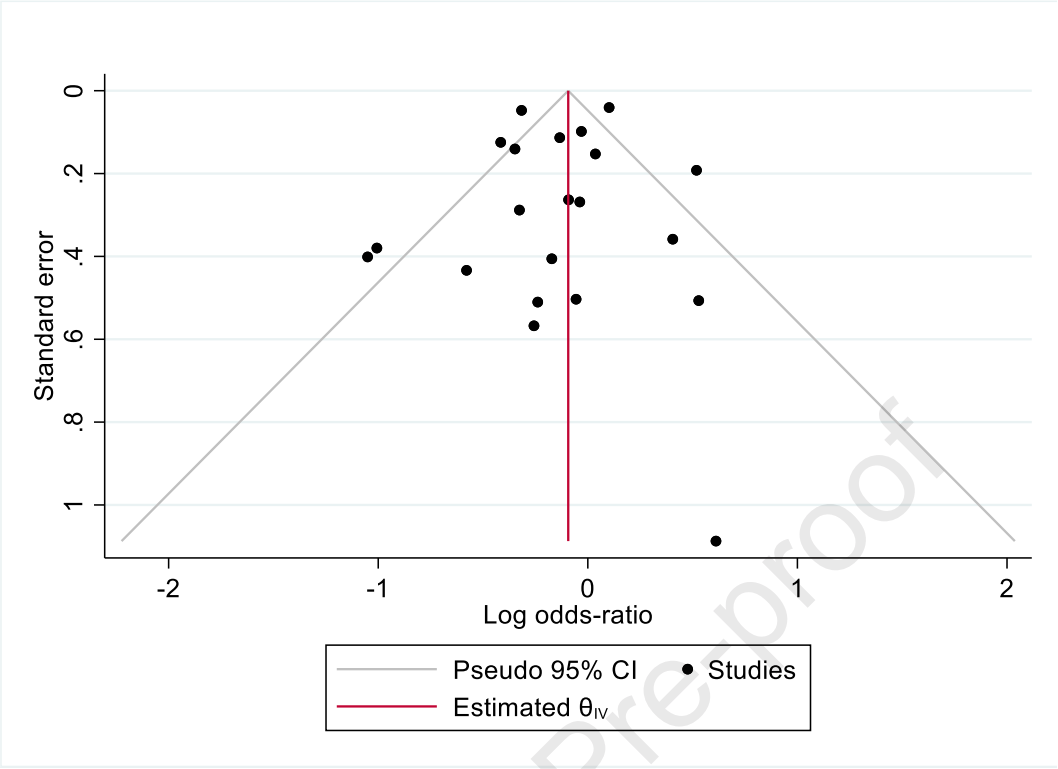
Abbreviations: CI, confidence interval; n, number

Supplementary figure 17. Association between baseline low grade dysplasia compared with non-dysplastic Barrett's and post-endoscopy esophageal cancer and neoplasia



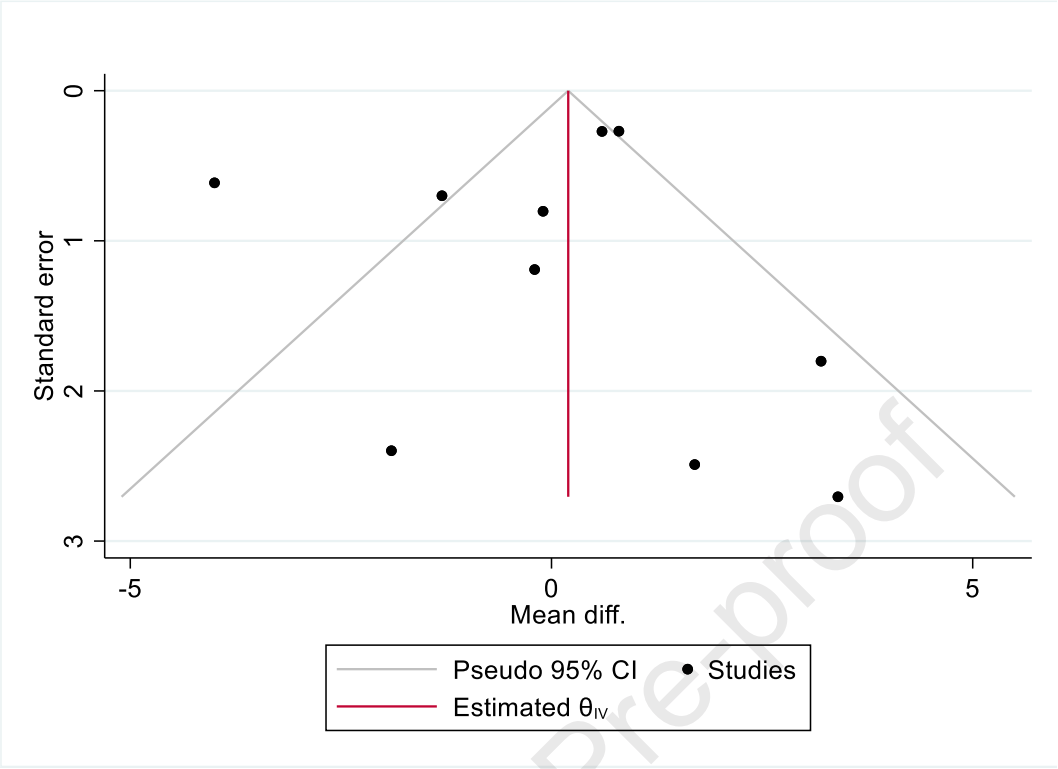
Abbreviations: LGD, low grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; post-endoscopy esophageal cancer; PEEN, Post-endoscopy esophageal neoplasia;
Patients with newly diagnosed BE with either LGD at baseline or NDBE were rescoped within one year and rates of PEEC (EAC) and PEEN (HGD/EAC) were quantified.

Supplementary figure 18. Funnel plot of sex comparisons between post-endoscopy and initially detected upper gastrointestinal cancers



Egger regression test: P = 0.754

Supplementary figure 19. Funnel plot of age at diagnosis comparisons between post-endoscopy and initially detected upper gastrointestinal cancers



Egger regression test: P = 0.310

Supplementary analysis 1. Funnel plot of age at diagnosis comparisons between post-endoscopy and initially detected upper gastrointestinal cancers

During the time periods over which patients in individual studies were recruited, endoscope technology has dramatically improved. Early populations included patients examined with fiberscopes[54], and in addition modern video endoscopes have improved over time in terms of resolution. Although our systematic review did not demonstrate an association high-resolution endoscope use and the PEUGIC vs. detected cancers, this analysis was limited to two relatively small studies. We are therefore unable to exclude the plausible relationship between endoscope resolution and PEUGIC rates at a population level. It is also not clear whether endoscope technology could influence the effect sizes for individual characteristics in PEUGIC/detected cancer comparisons. To indirectly assess these points we undertook a post-hoc analysis to establish whether the earliest and last year of participant recruitment in each study was independently associated with (i) prevalence of PEUGIC in the studied population; (ii) the mean difference in age at diagnosis between PEUGIC and detected cancers; (iii) the sex distribution of PEUGIC vs. detected cancers; and (iii) cancer staging of PEUGIC vs. detected cancers (for stage I to III vs. IV). The latter three factors were selected as they were the comparisons with the highest numbers of contributing studies. We conducted multivariable metaregression, indication for the EGD (unselected cohort, screening and Barrett's esophagus surveillance), maximum duration of the exposure window for PEUGIC applied in individual studies (for example a window between 6-36 months was considered as a 30 month window) and the time interval after a cancer-negative EGD used to define PEUGIC and the cancer(s) studied (esophageal, gastric or a combination of upper gastrointestinal cancers).

Year of earliest

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Table 1. Characteristics of selected studies

First author, year	Country	Setting	Study design	Population	Important characteristics	Recruitment period	Cancer site	Total EGDs	Total cancers	Total PEUGIC	Male, %	Mean age, y	PEUGIC definition, mo	Median interval, mo
Beck, 2021	Norway	PB	RC	Unselected	-	2007-2016	GC	NR	730	67	61.2	73[a]	6-36[b]	17.5[c]
Januszewicz, 2021	Poland	PB	RC	Unselected	-	2012-2018	EC, GC, DC	5877674	33241	1993	60.4	68.2	6-36	16.7[c]
Vajravelu, 2021	US	PB	RC	Surveillance	NDBE IM at baseline	2004-2019	EC (EAC)	NR	366	50	74	NR	1-12[d]	3.3
Dhaliwal, 2020	US	PB	RC	Surveillance	NDBE IM at baseline	1991-2019	EC (EAC)	NR	22	2	NR	NR	<12[d]	NR
Gavric, 2020	Slovenia	SC	RC	Unselected	Exc. Barrett's cohort	2007-2015	EC, GC	29617	422	29	64.3	70.6	<36	11
Januszewicz, 2019	Poland	MC	RC	Unselected	-	2002-2015	GC	29634	350	36	NR	NR	1-36	10.8
Delgado Guillena, 2019	Spain	MC	RC	Unselected	-	2012-2016	GC	NR	187	17	58	72.1	<36	6.5
Hernanz, 2019	Spain	MC	RC	Unselected	-	2008-2015	GC	123395	1288	61	60.6	69.3	<36	13.1
Tai, 2019	UK	SC	CC	Unselected	Exc. GU/DU FU	2012-2017	EC, GC	60214	672	48	62.1	72.1[e]	<36	18.3
van Putten, 2018	NI	PB	RC	Surveillance	NDBE (+/- IM)	1993-2010	EC (EAC)	NR	210	26	76.4[f]	66.9[a]	3-12[d]	NR
Rodríguez de Santiago, 2018	Spain	MC	RC	Unselected	Exc. Barrett's cohort	2008-2015	EC	123395	391	25	84	66.7	<36	18.6
Leung, 2018	Taiwan	PB	RC	Unselected	Routine diagnostic	2002-2007	GC	NR	20066	3303	66.4	67.6	6-24	NR
Iida, 2018	Japan	SC	CC	Screening	≥ 60 yrs	1997-2015	GC	NR	240	14	61[e]	72[e]	≤24[g]	NR
Jin, 2018	Korea	SC	CC	Screening	Exc. gastric adenoma	2014-2016	GC	NR	843	486	70.8	63.9	12-36	NR
Wang, 2016	US	PB	CC	Unselected	Exc. ≥ 2 EGDs in 3 yrs	2000-2007	EC, GC	NR	751	52	51.9	77.2	6-36	NR
Cheung, 2016	UK	PB	CC	Unselected	Exc. Barrett's cohort	2002-2012	EC, GC	NR	9487	633	58.6	70.2	12-36	NR
Hamashima, 2015	Japan	PB	RC	Screening	40-79 yrs	2001-2008	GC	NR	347	23	52.2	NR	<12	NR
Chadwick, 2015	UK	PB	CC	Unselected	-	2011-2012	GC	NR	2727	225	56	NR	3-36	NR
Cho, 2015	Korea	SC	CC	Screening	-	2006-2013	GC	NR	284	52	76.9	65.2	<24[g]	12.6[c]
Chadwick, 2014	UK	PB	CC	Unselected	-	2011-2012	EC	NR	6943	537	70.2	70.6[e]	3-36	NR
Raftopoulos, 2010	Australia	SC	RC	Unselected	Exc. Barrett's cohort	1990-2004	EC, GC, DC	28064	822	55	79.3	66.5	<12	4.16
Hosokawa, 2007	Japan	SC	CC	Unselected	-	1990-1998	GC	51411	730	188	75.5	NR	<36	NR
Bloomfield, 2005	US	SC	CC	Unselected	Exc. Barrett's cohort	1997-2001	EC	NR	110	10	90	57.2	<24	6
Yalamarthi, 2004	UK	SC	CC	Unselected	-	1994-2001	EC, GC	NR	305	30	NR	NR	<36	7.5
Hosokawa, 2001	Japan	SC	CC	Unselected	22.7% screening	1993-1996	GC	15579	269	32	68.8	60.3[h]	<36	NR

Abbreviations: CC, Case-control study; DU; duodenal ulcer; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; GU, gastric ulcer; HGD, HGD; IM; intestinal metaplasia; MC, multi-centre; mo, months; NA, not applicable; NDBE, non-dysplastic Barrett's esophagus; NI, Northern Ireland; NR, not reported; PB, population based; PEEN, Post-

endoscopy esophageal neoplasia; PEUGIC, post-endoscopy upper gastrointestinal cancer; RC, retrospective cohort; SC, single centre; UK, United Kingdom; US, United States; yrs, years.

Unselected cohorts comprised EGDs performed for a mixture of indications (including diagnostic, therapeutic, surveillance and screening); surveillance cohorts were for Barrett's esophagus surveillance; screening cohorts were for gastric cancer screening.

Sex and age presented where available for the PEUGIC group

[a]Median reported where mean not available

[b]In 3 patients with ≥ 3 EGDs with biopsies in the 6 months prior to diagnosis were not considered missed cancers.

[c]Mean reported where median not available

[d]From the date of diagnosis of Barrett's esophagus

[e]applicable to whole cohort with upper gastrointestinal cancer

[f]% male in the PEEN group (HGD/EAC as composite outcome)

[g]in addition status as "missed" based on review of prior endoscopy reports.

[h]Mean age at initial cancer-negative endoscopy

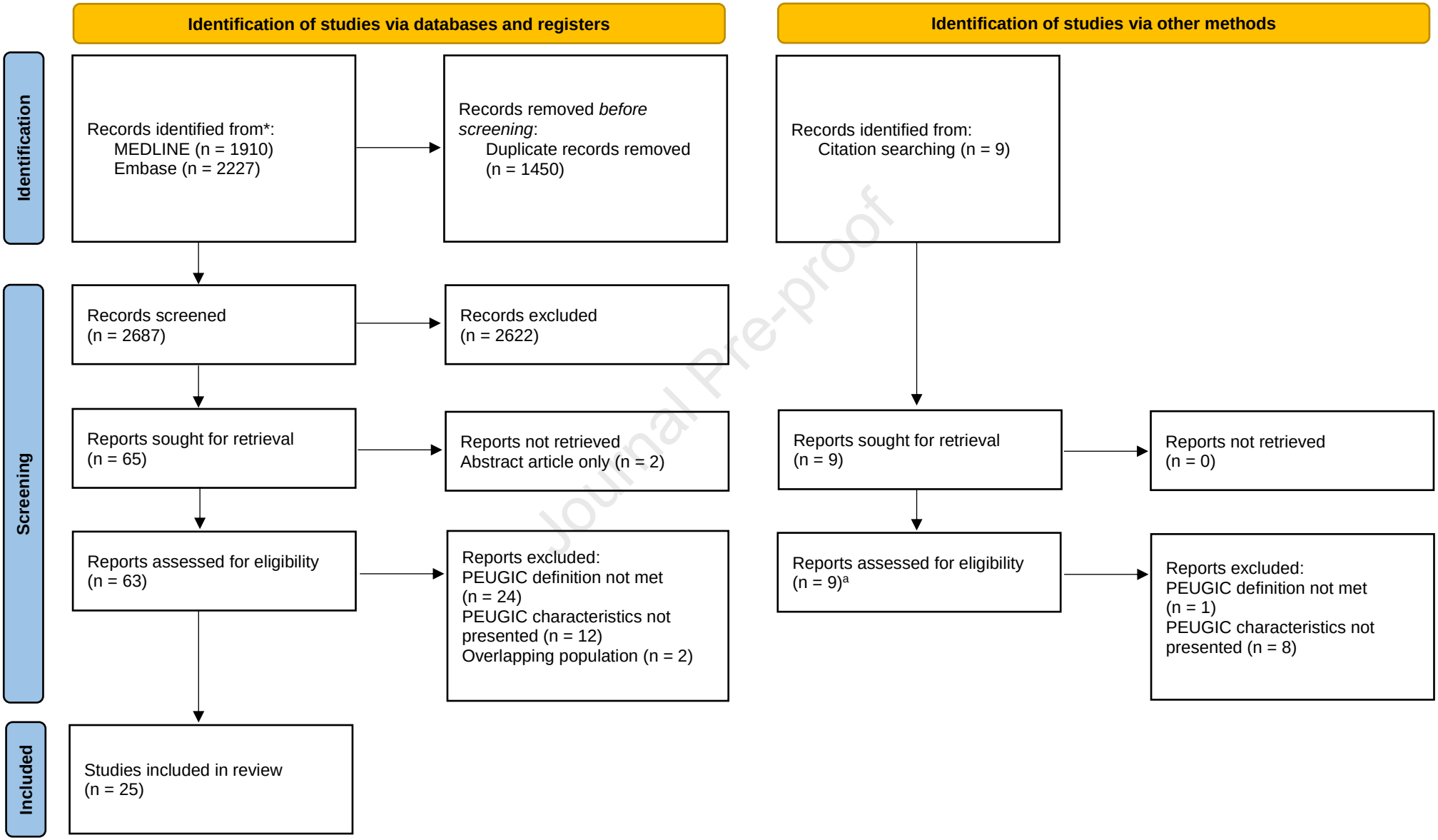
Table 2. Meta-analysis of characteristics of post-endoscopy and initially detected upper gastrointestinal cancers stratified by primary tumor site.

	Esophageal cancer					Gastric cancer					
Factor	**Studies / Estimates**	**PEEC n/total**	**Detected n/total**	**Effect size (95% CI)**	***I²***	**Studies / Estimates**	**PEGC n/total**	**Detected n/total**	**Effect size (95% CI)**	***I²***	**$P_{interaction}$**
Demographic											
Age[a]	2/2	299	5278	0.32 (-4.06-4.70)	64.7%	5/5	4223	19767	-0.54 (-2.91-1.83)	91.8%	0.733
Male	6/6	617/921	8695/12396	0.75 (0.55-1.03)	55.0%	11/11	3168/4804	16123/25196	0.95 (0.79-1.14)	66.1%	0.203
Clinical											
Any alarm symptoms	1/1	62/279	2650/4959	0.25 (0.19-0.33)	-	3/3	113/432	2443/5293	0.42 (0.32-0.54)	2.9%	0.009
Dysphagia	3/3	45/349	2522/5524	0.20 (0.10-0.41)	67.0%	3/3	27/443	540/5428	0.59 (0.40-0.89)	0.0%	0.009
Weight loss	3/3	16/349	291/5524	0.75 (0.37-1.51)	36.3%	2/2	8/382	220/4200	0.39 (0.19-0.79)	0.0%	0.201
Anemia	3/3	37/349	379/5524	1.28 (0.88-1.86)	0.0%	2/2	16/382	544/4200	0.29 (0.18-0.49)	0.0%	<0.001
Anorexia	1/1	4/279	102/4959	0.69 (0.25-1.89)	-	1/1	7/354	131/3895	0.58 (0.27-1.25)	-	0.783
Vomiting	2/2	10/299	358/5278	0.97 (0.33-2.87)	64.2%	3/3	23/443	531/5428	0.84 (0.29-2.41)	73.2%	0.847
Abdominal mass	1/1	2/279	22/4959	1.62 (0.38-6.93)	-	1/1	5/354	64/3895	0.86 (0.34-2.14)	-	0.468
Hematemesis/melena	2/2	12/299	135/5278	1.60 (0.87-2.91)	0.0%	3/3	29/443	389/5428	1.10 (0.57-2.11)	51.1%	0.408
Reflux	2/2	163/329	1282/5205	2.66 (2.11-3.35)	0.0%	1/1	142/354	793/3895	2.62 (2.09-3.29)	-	0.923
PPI therapy	1/1	18/25	147/366	3.83 (1.56-9.40)	-	1/1	48/61	569/1228	4.13 (2.47-6.88)	-	0.844
Endoscopic/procedural											
High-definition endoscope	1/1	15/25	250/366	0.70 (0.30-1.60)	-	1/1	22/61	500/1228	0.82 (0.48-1.40)	-	0.742
Inpatient setting	1/1	51/452	594/5765	1.11 (0.82-1.50)	-	1/1	43/191	528/2212	0.93 (0.65-1.32)	-	0.454
Experienced endoscopist	1/1	13/25	71/366	4.50 (1.97-10.28)	-	3/3	119/301	691/2002	0.85 (0.45-1.62)	78.7%	0.002
H. Pylori	-	-	-	-	-	3/3	57/130	855/1629	0.93 (0.36-2.39)	66.6%	-
Tumour-related											
Stage 1 vs. 2-4	3/3	82/374	172/4847	5.55 (2.04-15.11)	43.3%	6/6	487/775	832/4168	2.24 (1.57-3.19)	46.4%	0.094
Stage 1-2 vs. 3-4	3/3	202/374	1225/4847	3.43 (2.77-4.26)	0.0%	4/4	545/744	1215/3821	2.29 (1.34-3.89)	82.5%	0.164
Stage 1-3 vs. 4	2/2	288/368	3022/4810	2.21 (1.71-2.85)	0.0%	4/4	585/705	1835/3432	1.77 (1.01-3.12)	77.4%	0.487
Upper esophagus	6/6	71/719	872/9981	1.37 (1.05-1.79)	0.0%	-	-	-	-	-	-
Mid esophagus	6/6	186/719	4132/9981	0.92 (0.45-1.88)	86.9%	-	-	-	-	-	-
Lower esophagus	6/6	312/719	4171/9981	0.89 (0.65-1.23)	39.0%	-	-	-	-	-	-
Gastroesophageal junction	2/2	150/562	2151/6772	0.77 (0.64-0.94)	0.0%	-	-	-	-	-	-
EAC vs. ESCC	5/5	462/825	5857/12376	1.14 (0.89-1.47)	31.2%	-	-	-	-	-	-
Proximal gastric	-	-	-	-	-	10/10	354/1267	5891/17594	0.91 (0.74-1.10)	21.7%	-
Medial gastric	-	-	-	-	-	10/10	562/1267	7407/17594	1.29 (1.01-1.64)	57.3%	-
Distal gastric	-	-	-	-	-	10/10	344/1267	4205/17594	0.92 (0.75-1.12)	37.8%	-
Flat/sessile[b]						2/2	74/113	548/1460	1.78 (0.88-3.57)	53.2%	

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; n, number; PEEC, post-endoscopy esophageal cancer; PEGC, post-endoscopy gastric cancer; PPI, Proton pump inhibitor.

[a]Effect size expressed as mean difference. All other effect sizes expressed as odds ratios; [b]compared with sessile/mass

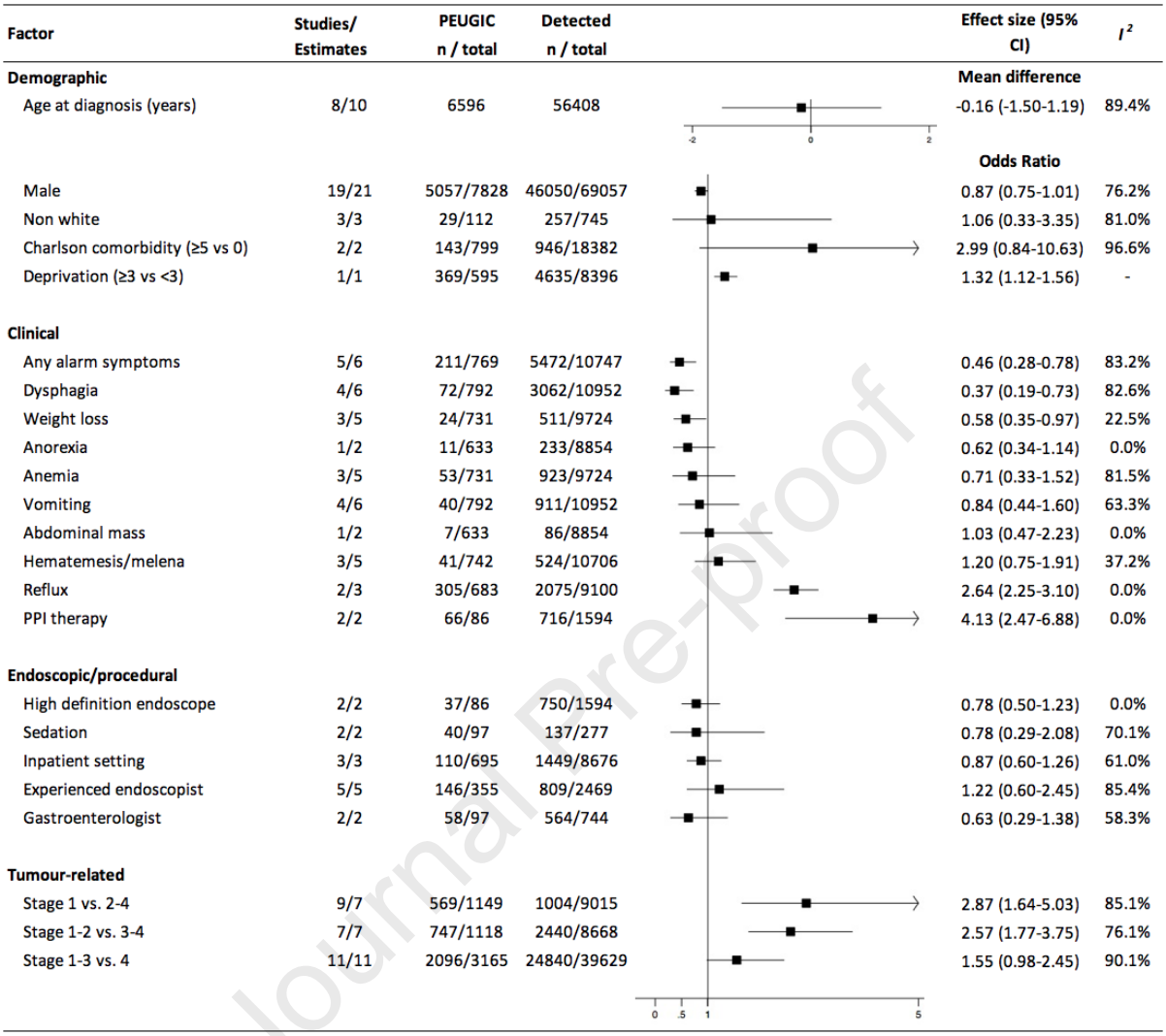
Figure 1. PRISMA Flow Diagram



Abbreviations: PEUGIC, post-endoscopy upper gastrointestinal cancer

[a]Citation searching did not highlight any studies eligible for inclusion

Figure 2. Meta-analysis of demographic, clinical, endoscopic/procedural and tumour-related characteristics in patients with post-endoscopy versus detected upper gastrointestinal cancers



Factor	Studies/ Estimates	PEUGIC n / total	Detected n / total	Effect size (95% CI)	I^2
Demographic				**Mean difference**	
Age at diagnosis (years)	8/10	6596	56408	-0.16 (-1.50-1.19)	89.4%
				Odds Ratio	
Male	19/21	5057/7828	46050/69057	0.87 (0.75-1.01)	76.2%
Non white	3/3	29/112	257/745	1.06 (0.33-3.35)	81.0%
Charlson comorbidity (≥5 vs 0)	2/2	143/799	946/18382	2.99 (0.84-10.63)	96.6%
Deprivation (≥3 vs <3)	1/1	369/595	4635/8396	1.32 (1.12-1.56)	-
Clinical					
Any alarm symptoms	5/6	211/769	5472/10747	0.46 (0.28-0.78)	83.2%
Dysphagia	4/6	72/792	3062/10952	0.37 (0.19-0.73)	82.6%
Weight loss	3/5	24/731	511/9724	0.58 (0.35-0.97)	22.5%
Anorexia	1/2	11/633	233/8854	0.62 (0.34-1.14)	0.0%
Anemia	3/5	53/731	923/9724	0.71 (0.33-1.52)	81.5%
Vomiting	4/6	40/792	911/10952	0.84 (0.44-1.60)	63.3%
Abdominal mass	1/2	7/633	86/8854	1.03 (0.47-2.23)	0.0%
Hematemesis/melena	3/5	41/742	524/10706	1.20 (0.75-1.91)	37.2%
Reflux	2/3	305/683	2075/9100	2.64 (2.25-3.10)	0.0%
PPI therapy	2/2	66/86	716/1594	4.13 (2.47-6.88)	0.0%
Endoscopic/procedural					
High definition endoscope	2/2	37/86	750/1594	0.78 (0.50-1.23)	0.0%
Sedation	2/2	40/97	137/277	0.78 (0.29-2.08)	70.1%
Inpatient setting	3/3	110/695	1449/8676	0.87 (0.60-1.26)	61.0%
Experienced endoscopist	5/5	146/355	809/2469	1.22 (0.60-2.45)	85.4%
Gastroenterologist	2/2	58/97	564/744	0.63 (0.29-1.38)	58.3%
Tumour-related					
Stage 1 vs. 2-4	9/7	569/1149	1004/9015	2.87 (1.64-5.03)	85.1%
Stage 1-2 vs. 3-4	7/7	747/1118	2440/8668	2.57 (1.77-3.75)	76.1%
Stage 1-3 vs. 4	11/11	2096/3165	24840/39629	1.55 (0.98-2.45)	90.1%

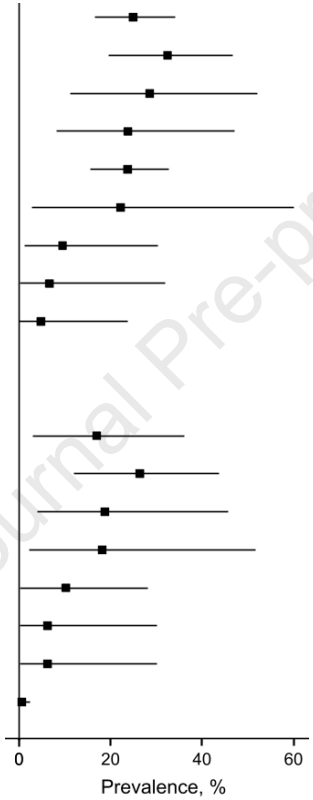
Abbreviations: EC, esophageal cancer; GC, gastric cancer; n, number; PEUGIC, post-endoscopy upper gastrointestinal cancer; PPI, Proton pump inhibitor

Deprivation measured using Townsend deprivation index in quintiles (3^{rd} – 5^{th} vs. 1-2^{nd})

Charlson comorbidity score (each co-morbidity assigned a weight from 1 – 6).

Figure 3. Meta-analysis of proportions of findings in the "cancer-negative" esophagogastroduodenoscopy preceding diagnosis of PEUGIC

Finding	Studies	PEUGIC		Proportion, % (95% CI)	I^2
		n	total		
Gastric cancer					
Normal	3	26	103	24.9% (16.7%-34.1%)	0.0%
Gastritis	5	123	466	32.5% (19.6%-46.7%)	75.4%
Erosions	1	6	21	28.6% (11.3%-52.2%)	-
Intestinal metaplasia	1	5	21	23.8% (8.2%-47.2%)	-
Gastric ulcer	3	25	103	23.7% (15.6%-32.7%)	0.0%
Suspicious gastric lesion	1	2	9	22.2% (2.8%-60.0%)	-
Hiatus hernia	1	2	21	9.5% (1.2%-30.4%)	-
Gastric atrophy	1	1	15	6.7% (0.2%-32.0%)	-
Gastric polyp	1	1	21	4.8% (0.1%-23.8%)	-
Esophageal cancer					
Normal	3	6	29	17.0% (3.1%-36.1%)	0.0%
Esophagitis	3	64	306	26.4% (12.0%-43.7%)	59.6%
Food bolus	1	3	16	18.8% (4.1%-45.7%)	-
Hiatus hernia	1	2	11	18.2% (2.3%-51.8%)	-
Esophageal stricture	3	17	306	10.3% (0.3%-28.1%)	72.6%
Esophageal candidiasis	1	1	16	6.3% (0.2%-30.2%)	-
Schatzski ring	1	1	16	6.3% (0.2%-30.2%)	-
Esophageal ulcer	2	5	295	0.6% (0.0%-2.3%)	0.0%



Abbreviations: n, number; PEUGIC, post-endoscopy upper gastrointestinal cancer.
Endoscopic findings reported for PEUGIC diagnosed 6-36 months after a "cancer-negative" endoscopy. Site-specific findings reported only.

Title: Clinical and Endoscopic Characteristics Associated with Post-Endoscopy Upper Gastrointestinal Cancers: a Systematic Review and Meta-analysis

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CRediT Authorship contributions: Leo Alexandre: Conceptualization, Methodology, Software, Data Curation, Formal analysis, Visualization, Project administration, Supervision, Writing – Original Draft; Theo Tsilegeridis-Legeris: Investigation, Writing – review & editing; Stephen Lam: Investigation, Writing – review & editing.

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Abstract

Background and aims: Ten percent of patients with an upper gastrointestinal cancer will have received an esophagogastroduodenoscopy (EGD) within three years prior to diagnosis, termed post-endoscopy upper gastrointestinal cancers (PEUGIC). We aimed to determine the characteristics of PEUGIC, and compare these with detected cancers.

Methods: We searched MEDLINE and Embase from inception for studies comparing the characteristics of PEUGIC and detected UGI cancers, and reported findings at the initial "cancer-negative" endoscopy. We synthesised results using random effects meta-analysis. This review is registered on PROSPERO, CRD42019125780.

Results: A total of 2696 citations were screened and 25 studies were included, comprising 81184 UGI cancers, of which 7926 were considered PEUGIC. For PEUGIC assessed within 6-36 months of a "cancer-negative" EGD the mean interval was approximately 17 months. Patients with PEUGIC were less likely to present with dysphagia (OR 0.37) and weight loss (OR 0.58) and were more likely to present with gastro-esophageal reflux (OR 2.64) than detected cancers. PEUGIC were more common in women in Western populations (OR 1.30). PEUGIC were typically smaller at diagnosis and associated with less advanced disease staging compared with detected cancers (OR 2.87 for stage 1 vs. 2-4). Most EGDs (>75%) were abnormal preceding diagnosis of PEUGIC.

Conclusions: There is a substantial delay in the diagnosis of PEUGIC. They are less likely to present with alarm symptoms than detected cancers. PEUGIC are overall less advanced at diagnosis. The majority with PEUGIC have abnormalities reported at the preceding "cancer negative" EGD. The epidemiology of PEUGIC may inform preventive strategy.

Keywords: PEEC; PEGC; missed lesions; quality indicators

Introduction

Worldwide, in 2018 there were over 1.5 million incident cases of esophago-gastric cancer, and nearly 1.3 million associated deaths[1]. Most patients are diagnosed with advanced disease and their overall prognosis is poor[2]. Esophagogastroduodenoscopy (EGD) is the mainstay of diagnosis, however not all cancers in the upper gastro-intestinal (UGI) tract are detected initially. UGI cancers diagnosed within three years of a "cancer negative" endoscopy, are generally considered post-endoscopy UGI cancers (PEUGIC)[3, 4]. On average, for every 400 gastroscopies performed, one will miss an UGI cancer[5]. A meta-analysis of international studies demonstrated 11.3% (95% CI 7.5 – 16.6%) of patients with UGI cancer had undergone an EGD in the preceding 3 years, with substantial variation in the estimated prevalence between studies[5]. Insights into the epidemiology of post-colonoscopy colorectal cancer (PCCRC) have led to improved understanding of their aetiology, which has led to initiatives to reduce their incidence[6-8]. In comparison, the aetiology of PEUGIC is relatively poorly understood. The implications of initially failing to detect an UGI cancer are potentially serious: if the interval is significant, in the context of an aggressive epithelial malignancy, treatment options and prognosis may become more limited; and there may be associated healthcare cost implications. Understanding of the epidemiology of PEUGIC is therefore important, and a prerequisite for devising strategy to reduce their incidence.

The aims of this systematic review and meta-analysis were to (1) determine the demographic, clinical, endoscopic/procedural and tumor-related characteristics of PEUGIC, and compare these with initially detected cancers (those diagnosed with UGI cancer without a preceding EGD within three years); and (2) determine the prevalence of individual endoscopic findings at the initial "cancer-negative" endoscopy in patients diagnosed subsequently with PEUGIC.

Materials and Methods

The protocol for this systematic review was registered on the PROSPERO database (reference, CRD42019125780) and conducted in accordance with the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[9].

Definitions

We defined PEUGIC as any upper GI malignancy diagnosed within three years of a "cancer-negative" endoscopy[3]. This term is intended to encompass both post-endoscopy esophageal cancer (PEEC) and post-endoscopy gastric cancer (PEGC)[4]. We also considered post-endoscopy esophageal neoplasia (PEEN) (a composite outcome of high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC) in Barrett's esophagus cohorts. We considered PEEC or PEEN in BE cohorts as an outcome if patients were rescoped within one year of BE diagnosis, in line with recent research[10, 11]. We defined initially detected malignancies in the upper GI tract those diagnosed in the absence of a preceding cancer-negative endoscopy or the presence of such an endoscopy either within three to six months or greater than three years previously.

Search strategy

We sought relevant published articles and abstracts by searching MEDLINE and EMBASE from inception using the OVID interface (the search strategy is detailed in supplementary table 1), and manual searches of reference lists of relevant contemporaneous systematic reviews[10, 11]. No language restrictions were placed on the searches. Searches were up to date as of 22 November 2021.

Eligibility criteria

Cohort and case-control studies satisfying the following eligibility criteria were included: (i) PEUGIC defined as UGI cancers diagnosed up to three years after a "cancer-negative" endoscopy; (ii) demographic, clinical, endoscopic/procedural or tumor-related data presented for those with PEUGIC at the point of diagnosis or at the time of the preceding "cancer-negative" endoscopy; (iii) either (a) report sufficient data to compare any of characteristics listed in (ii) for PEUGIC with either detected cancers or those with "cancer-negative" endoscopy which did not herald PEUGIC or (b) data to calculate the prevalence of endoscopic findings at the initial "cancer-negative" endoscopy for the PEUGIC group; (iv) EGD performed for any indication. Studies were ineligible if they included the following: (i) purely surgical or endoscopic submucosal dissection cohorts; (ii) radiologically screened populations; (iii) missed synchronous cancer as the primary outcome; and (iv) BE-HGD at baseline.

Two reviewers (LA and SL) independently screened abstracts and selected full text articles for inclusion based on the above criteria. Discrepancies were resolved through discussion between reviewers.

Data extraction and quality assessment

Two reviewers (LA and TTL) independently extracted data from each selected article for study characteristics (study design, location, recruitment period, sample size, definition of PEUGIC used, sites and PEUGIC frequency); demographic characteristics (sex, age, ethnicity); clinical characteristics (comorbidity, symptoms, proton pump inhibitor use, cancer staging); endoscopic/procedural characteristics (endoscopist specialty/experience, inpatient setting, high definition endoscope use, cancer location and findings at a "cancer-negative" endoscopy preceding PEUGIC diagnosis); histological findings. For studies that reported data for more than one time period elapsed after the first "cancer-negative" endoscopy (for example, 0-2 years and 0-4 years) to define PEUGIC, data were extracted for longest period within 3 years. Endoscopic findings at the "cancer-negative" endoscopy preceding PEUGIC were reported for those who were diagnosed six to 36 months after endoscopy. A modified Newcastle Ottawa Scale for cross-sectional studies[12] was adapted for the purpose of this systematic review, to appraise the internal validity of selected studies (Supplementary table 2) which compared characteristics of PEUGIC with detected cancers. Using this scale, studies were scored across four domains: selection (two questions); PEUGIC sample size (one question); PEUGIC definition (two questions) and outcome ascertainment (one question). Assessment for questions relating to statistical analysis were omitted as they were deemed not applicable to the research question. Therefore, for individual studies the highest possible score was ten points. Scores of 0 to 4, ≥5 to <7 and ≥7 to 10 were respectively assigned low, moderate and high quality. Discrepancies were resolved through consensus discussion between reviewers.

Statistical analysis

For the first aim we synthesized results using random-effects meta-analysis, using mean differences for continuous outcomes, and odds ratios (ORs) for binary outcomes, and present 95% confidence intervals. For these comparisons, the demographic, clinical, endoscopic/procedural and tumour-related characteristics (from hereon referred to as characteristics) of PEUGIC were compared with detected cancers; and to aid interpretation an OR < 1 indicates the characteristic has a lower odds of PEUGIC than detected UGI cancer (and vice versa). The primary outcome was PEUGIC: all UGI malignancies (esophageal, gastric and duodenal) were considered a composite outcome in meta-

analyses, as diagnoses of any of these is a key outcome and legitimate purpose of EGD. Secondary outcomes were PEGC and PEEC . Characteristics of PEUGIC and detected cancer populations were also compared in a number of stratified analyses: (1) by tumor site (esophageal vs. gastric cancer); (2) unselected cohorts vs. screening for the outcome of PEGC; (3) unselected cohorts vs. BE surveillance cohorts for the outcome of PEEC and (4) by geographic location (Western vs. Australasian populations) for sex comparisons with PEUGIC as the outcome. To determine the robustness of study findings to assumptions underlying the definition of PEUGIC sensitivity analyses compared characteristics of PEUGIC and detected cancer populations by varying (1) the upper limit of the interval used to define PEUGIC (diagnosis of UGI cancer with < 12, <24 and <36 months of a cancer-negative EGD) in all cohorts; and (2) lower limit of the of the interval used to define PEUGIC (at least 6 months after cancer-negative EGD excluded vs. 0 to 3 months excluded after diagnosis). Tests for interaction were applied across strata to explore reasons for statistical heterogeneity, with $P_{interaction}$ <0.1 regarded as statistically significant. For the second aim we performed a meta-analysis of proportions of endoscopic findings for the "cancer-negative" findings prior to PEUGIC, stratified by cancer site (esophageal and gastric) extracted from each study. We used the STATA program, *metaprop*[13] for this purpose. Presented confidence intervals for individual studies were calculated using the binomial exact method[14]. Proportions were transformed to stabilize their variances using Freeman-Tukey double arcsine transformation[15], prior to calculation of pooled estimates using the random effects model proposed by DeSimonian and Laird[16]. Confidence intervals for the pooled estimates were calculated using the Wald method. We estimated the percentage of variation across all studies due to heterogeneity using I^2; with values of 25%, 50% and 75% respectively indicating low, moderate and high heterogeneity. Small-study effects were evaluated visually using a funnel plot and Egger's regression for comparisons with at least 10 estimates. Meta-regression analysis estimated the linear association between quality assessment scores and (i) prevalence of POUGIC; and (ii) sex comparisons between PEUGIC and detected cancers across all studies. Multivariable meta-regression analysis investigated whether the upper and lower limitis of the recruitment window (in calendar years) were associated with PEUGIC prevalence and clinical characteristics in PEUGIC (vs. detected cancer) comparisons (detailed in supplementary table 9). Analyses were performed with STATA version 17 (StataCorp LP, College Station, Texas, USA).

Results

Search and Selection of Studies

Among 2, 696 articles identified from the literature search, 72 full-text articles were assessed for eligibility, of which 25 were ultimately eligible for inclusion (Figure 1)[17-41]. The 47 excluded articles were rejected on the basis the specified definition for PEUGIC was not met (n = 25), characteristics of PEUGIC at diagnosis or the findings of the preceding cancer-negative endoscopy were not presented (n = 20), and two included overlapping data from studies already selected (supplementary table 3).

Study Characteristics

The characteristics of selected studies are shown in Table 1. Thirteen were from Europe[17, 19-21, 23, 25, 27, 31, 32, 36, 37, 39, 41], four were from the United States[18, 24, 38, 40], seven were from Asia[22, 26, 28-30, 33, 34] and a single study was from Australia[35]. Eleven were population-based[17, 19-21, 24, 26, 32, 34, 38-40], four were multi-center[23, 27, 31, 36] and ten were single-centre studies[18, 22, 25, 28-30, 33, 35, 37, 41]. Thirteen were retrospective cohort studies[17, 23-27, 31, 32, 34-36, 38, 39], and the remaining 12 were case-control studies[18-22, 28-30, 33, 37, 40, 41]. Three of the selected studies were from gastric cancer screening programs[26, 30, 33]; three were from BE surveillance cohorts[24, 38, 39], and the remaining 19 were from unselected cohorts performed for a variety of indications[17-23, 25, 27-29, 31, 32, 34-37, 40, 41]. Characteristics of post-endoscopy esophageal, gastric and duodenal cancers were respectively reported in 13 studies[18, 19, 21, 24, 25, 32, 35-41], 19 studies[17, 20-23, 25-35, 37, 40, 41] and two studies[32, 35]. From a total of 81, 184 UGI cancers, 7, 926 were considered PEUGIC (pooled prevalence 10.7%, 95% CI 8.0 – 13.7% overall) excluding overlapping populations, including 1333 PEEC (7.0%, 95% CI 5.6 – 8.6%) (of which 552 were EAC and 378 were ESCC, where histology was known), 6560 PEGC (11.9%, 95% CI 8.3 – 16.1%) and 43 post-endoscopy duodenal cancers. (supplementary figure 1-3). Sixteen studies considered 36 months as the upper limit for the definition of PEUGIC[17, 19-21, 23, 25, 27-29, 31-33, 36, 37, 40, 41], four considered 24 months[18, 22, 30, 34] and 5 considered 12 months[24, 26, 35, 38] (of which three were Barrett's cohorts). In those studies which considered 36 months as the upper limit, the reported median intervals ranged from 6.5 to 18.6 months[23, 28], and of these values, the median interval was 11 months. In terms of the period of time after the index EGD excluded in the definition of PEUGIC, 14 excluded no time period[18, 22-30, 35-37, 41], two excluded one month[31, 38], four excluded three months[19, 20, 39, 40] and five excluded six months or more[17, 21, 32-34]. In total, three studies considered a definition for PEUGIC as six to 36 months following a cancer-negative endoscopy[17, 32, 40], with a mean interval until diagnosis of 16.7 (SD 8.5) and 17.5 (SD 8.8) months reported by two[17, 32].

Demographic characteristics

Figure 2 summarises the meta-analyses (shown individually in supplementary figures 4-12) of the demographic, clinical and endoscopic/procedural and tumor-related characteristics of PEUGIC. Overall there were no significant differences in age at diagnosis (mean difference -0.16, 95% CI -1.50 to 1.19 years). There was some evidence that men have a lower odds of PEUGIC than women (OR 0.87, 95% CI 0.75-1.01, p = 0.07) overall. On subgroup analysis (supplementary figure 6), this observation was confirmed in Western populations (OR 0.77, 95% CI 0.75-0.86). One study demonstrated that PEUGIC were more common in more deprived groups[21].

When stratifying effect sizes by tumor site (esophageal vs. gastric) and PEGC population (unselected vs. screened) there were no significant differences for age at diagnosis or sex (table 2 and supplementary table 4); however for comparisons of PEEC (unselected cohorts vs. BE surveillace cohorts, supplementary table 5) male sex was inversely associated in BE populatons (OR 0.37, 95% CI 0.32 to 0.77) with a significant interaction $P_{interaction}$ = 0.042). Furthermore, non-white ethnicity was associated with higher odds of PEEC in a single unselected cohort (OR 5.67, 95% CI 1.46-21.98)[40].

Clinical characteristics

Patients with PEUGIC had a lower odds of presenting with alarm symptoms than detected UGI cancers (OR 0.46, 95% CI 0.28-0.78), in particular dysphagia and weight loss (Figure 2, supplementary figures 9-10). Other clinical findings including anorexia, vomiting, hematemesis/malena, abdominal mass and anemia were not significantly associated with PEUGIC overall. PEUGUC were more commonly associated with reflux (OR 2.64, 95% CI 2.25-3.10) and proton pump inhibitor (PPI) use (OR 4.13, 95% CI 2.47-6.88), an observation seen in both PEEC and PEGC individually, an observation limited to two studies[27, 36].

On subgroup analysis, there were significant interactions for particular clinical characteristics (alarm symptoms overall, dysphagia and anemia), when starifying by tumor site (table 2). Individually, PEEC and PEGC were less commonly associated with any alarm symptoms, however the strongest inverse associations were observed with esophageal cancers (OR 0.25, 95% CI 0.19-0.33 vs. OR 0.42, 95% CI 0.32-0.54 with gastric cancers; $P_{interaction}$ = 0.009). The inverse association between dysphagia and PEEC (OR 0.20, 95% CI 0.10-0.41) was stronger ($P_{interaction}$ < 0.009) than for PEGC (OR 0.59, 95% CI 0.40-0.89). PEGC was less commonly associated with anemia (OR 0.29, 95% CI 0.18-0.49), than detected gastric cancers, and differed to esophageal cancer ($P_{interaction}$ < 0.001) for which there was no significant association. There was a significant interaction in effect sizes for dysphagia between PEEC in

unselected cohorts (OR 0.14, 95% CI 0.10-0.20) compared to a BE surveillance cohort (OR 0.35, 95% CI 0.18-0.68) ($P_{interaction}$ = 0.02).

Endoscopic/procedural characteristics

The use of a high definition endoscope, sedation, inpatient setting, an "experienced endoscopist" or gastroenterologist, were not significantly associated with PEUGIC (Figure 2, supplementary figure 11).

On subgroup analysis, in patients with esophageal cancer, EGD performed by an experienced endoscopist had a higher odds of PEUGIC (OR 4.50, 95% CI 1.97-10.28), an observation confined to a single study[36]; with no significant equivalent association observed in PEGC (OR 0.85, 95% CI 0.45-1.62) ($P_{interaction}$ = 0.002) (table 3). Gastric intestinal metaplasia (IM) was more commonly found at the time of index "cancer-negative endoscopy" in those with PEGC than those with detected UGI cancers (OR 4.85, 95% CI 1.86-12.69) (supplementary table 4), a finding confined to a single study in a screening population[22].

Tumor-related characteristics

Of studies which compared primary tumor size at diagnosis, both PEEC and PEGC were significantly smaller than initially detected cancers[22, 27, 33, 36]. Patients with PEUGIC generally presented with less advanced disease than detected cancers, for example, PEUGIC were more likely to present with stage 1 disease, vs. stage 2-4, (OR 2.87, 95% CI 1.64-5.03) (figure 2, table 2 and supplementary figure 12) than detected cancers, a finding observed in both PEEC and PEGC. Significant interactions for staging were noted between unselected and screened populations for the outcome of PEGC, where those in screened populations had higher odds of being diagnosed with early stage disease (supplementary table 4). Tumors in patients with PEGC were more likely to be localized to the gastric body than elsewhere (OR 1.29, 95% CI 1.01-1.64). PEEC more commonly presented in the upper esophagus (OR 1.37, 95% CI 1.05–1.79), and were less likely to present at the gastro-esophageal junction (GEJ) (OR 0.77, 95% CI 0.64-0.94) relative to detected cancers (however, in absolute tems 69% of all PEEC were localized to the mid or lower esophagus). In patients with gastric cancer, there were no differences in tumor morphology between PEGC and detected groups at the time of diagnosis. For esophageal cancer, there were no differences in the distribution of histological subtypes (adenocarcinoma and squamous cell carcinoma) between PEEC and detected groups.

PEUGIC definition sensitivity analyses

In analyses which stratified effects by the definition of PEUGIC (supplementary table 6) by mutually exclusive time intervals of < 12, < 24 and < 36 months, the associations observed for demographic,

clinical, endoscopic/procedural and tumor-related characteristics were mainly driven by those which considered the < 36 month time interval, and associations remained consistent with the main findings of this research. In analyses which stratified effects according to the interval after the cancer-negative endoscopy according to a 6 month threshold, characteristics were broadly consistent, with the exception of PEUGIC prevalence ($P_{interaction}$ = 0.08), vomiting ($P_{interaction}$ < 0.001) and the distribution of EAC vs. ESCC ($P_{interaction}$ = 0.019) (supplementary table 7).

Findings in the preceding cancer-negative endoscopy

Figure 3 (and supplementary figures 15 and 16) presents the meta-estimates of preceding endosopic findings for PEUGIC. With regard to PEGC, normal appearances at EGD were reported in 24.9% of the preceding "cancer-negative" procedures. IM, gastritis, erosions, gastric ulcer and "suspicious gastric lesions" were the most commonly reported abnormalities (22-32%) 6 to 36 months prior to diagnosis. Hiatus hernia, gastric atrophy and gastric polyp were less common (5-10%). With regard to PEEC, normal appearances at EGD were reported in 17%. The most common abnormality reported was esophagitis (26.4%). Other common abnormalities seen include food bolus obstruction, hiatal hernia and esophageal stricture (10-19%). Esophageal ulcer was an uncommon finding at the preceding endoscopy (0.6%).

Baseline histology and PEEC/PEEN in BE surveillance

Low-grade dysplasia diagnosed at baseline (n=77), compared with non-dysplastic BE (n=314) was not significantly associated with PEEC (n=2) (diagnosed within 1 year of BE diagnosis) (OR 4.12, 95% CI 0.25 to 66.6%); however was associated with PEEN (n=8) (OR 13.2, 95% CI 2.6-66.7) in a single study (supplementary figure 17)[24].

Study quality and small-study effects

Study-level risk of bias is summarized in supplementary table 8. Studies assessed scored between 4-10 (maximum score 10): 21 studies were deemed of high quality, three of moderate quality and one of low quality. All studies scored equally in terms of outcome ascertainment, though differed with respect to selection, sample size and the definition of PEUGIC. Quality assessment scores were not associated with either the prevalence of POUGIC (risk difference 1.3%, 95% CI -0.3 to 3%) or the effect size of male sex and odds of POUGIC (OR 0.98, 95% CI 0.87 to 1.11) per point increase in score. There was no evidence of small-study effects including publication bias on visual inspection of the funnel plots of sex and age comparisons (supplementary figures 18 and 19) or with Egger's regression (P = 0.754 and 0.310 respectively).

Discussion

This systematic review has demonstrated the demographic, clinical, endoscopic/procedural and tumor-related characteristics of patients with PEUGIC in comparison to detected cancers, and established the most common findings of "cancer-negative" endoscopies preceding diagnosis of PEUGIC. Delays in diagnosis are often substantial, with the median and mean time from cancer-negative endoscopy to diagnosis being 11 and approximately 17 months. PEUGIC are common and account for 10.7% of all UGI cancers. Age at the diagnostic procedure is similar between PEUGIC and detected UGI cancers. There is some evidence that women have a higher propensity to PEUGIC in Western populations. PEUGIC less commonly present with alarm symptoms. Anemia was less commonly noted in PEGC specifically. Reflux and PPI use are more commonly associated with PEUGIC. There is little evidence that use of high definition endoscope, sedation, an inpatient setting, clinician experience or primary specialty of the endscopist is associated with PEUGIC diagnosis. There is evidence that PEUGIC are smaller and are associated with generally less advanced tumor stage than detected cancers. PEEC more commonly present in the upper esophagus and were less commonly seen at the gastro-esophageal junction relative to detected cancers. There was no association between histological subtype and PEEC overall. Endoscopic abnormalities at the "cancer-negative" endoscopy preceding diagnosis of PEUGIC are common. The most frequent abnormalities (found in > 10% of cases) for gastric cancer are IM, gastritis, gastric ulcer, erosions, and a suspicious lesion; and for esophageal cancer are esophagitis, stricture, food bolus obstruction or hiatus hernia.

It is likely there are numerous and complex causal pathways which lead to UGI cancers not initially being detected on EGD. Previously cited explanations for PEUGIC include missing lesions (due to inadequate visualization of the mucosa, poor lesion recognition, insufficient biopsies from detected abnormalities, benign histology from detected abnormalities, pathology errors, and/or limited endoscopic image resolution), inadequate follow-up of lesions (e.g. esophageal or gastric ulcers), inadequate surveillance of premalignant lesions (especially BE), and *de novo* cancer development within three years of a "cancer-negative" EGD[5, 35, 36, 41]. Further insights may be gained following interpretation of the data presented here in clinical context. Some findings of this systematic review are consistent with the observation that PEUGIC (both PEEC and PEGC) are significantly smaller when measured endoscopically on average than detected tumors[22, 27, 33, 36]. Smaller primary UGI tumors at diagnosis are associated with less advanced tumor staging[42-44], a finding consistent with our systematic review as PEUGIC were more likely to present with less advanced disease. With a median delay of diagnosis of 11 months, such tumors would be expected to have been even smaller at the time of the

"cancer-negative" endoscopy, assuming they were present. A small tumor size (or a more subtle abnormality) at the time of a "cancer-negative" endoscopy preceding diagnosis represents a plausible and likely important explanation for not initially detecting an UGI cancer. This may also explain the disparity in symptom profile at diagnosis between PEUGIC and detected UGI cancers. The presence of alarm symptoms at diagnosis of UGI cancer is associated with larger primary tumors and more advanced disease[45], and could account for the lower prevalence of alarm symptoms than in those with PEUGIC. The association between reflux and PPI use and PEUGIC, may in part, be accounted for by the lower relative prevalence of alarm symptoms (even when acknowledging such symptoms are not necessarily mutually exclusive) among patients with PEUGIC. This observation may also be consistent with the frequent observation of esophagitis (26.4%) at EGD preceding PEEC diagnosis, although the relative importance of this finding is not known. The lower prevalence of anemia in PEGC, is consistent with the known associations between anemia and tumor size and more adanced cancer staging in those with gastric cancer[46, 47].

IM was highly prevalent at the "cancer-negative" EGD (90%) in one study preceding diagnosis of gastric cancer, and was strongly associated with PEUGIC[22]. While the role of IM as a precursor lesion to gastric cancer is established[48], and likely explains its high prevalence preceding PEGC diagnosis, the higher prevalence at the "cancer-negative" endoscopy preceding diagnosis could possibly be due to the greater clinical priority of establishing a tissue diagnosis from a visible tumor, rather than sampling adjacent non-malignant gastric mucosa, leading to detection bias. PEEC were more likely to be diagnosed in the upper esophagus than the middle and lower esophagus compared with detected esophageal cancers. The upper esophagus has previously been considered a higher risk location for not initially detecting cancer[49]. It is therefore of interest that our systematic review did not demonstrate evidence of a predilection of PEEC to be squamous cell cancers (vs. adenocarcinoma), compared with detected esophageal cancers. However, most PEEC were located in the mid or lower esophagus (69%) and tumor site was not stratified by (or mutually adjusted for) histological subtype - analysis which we speculate could be informative. It is also not clear why women were more likely to be diagnosed with PEUGIC than detected UGI cancers in the West. Future research is required to understand this discrepancy. Consistent with our systematic review, both female sex and increasing comorbidity are also associated with higher odds of post-colonoscopy colorectal cancer, for unclear reasons[8, 50].

Abnormalities preceding diagnosis of PEUGIC are very common. While some discrete findings (such as gastric ulcer, a suspicious gastric lesion, esophageal stricture or esophagitis) may plausibly directly

indicate unrecognised/undiagnosed cancer (prior to diagnosis of PEUGIC) and should arouse clinical suspicion, the other findings are potentially less specific. The association (with a measure of relative effect size) between each of these findings at the time of a "cancer-negative" EGD and subsequent diagnosis of PEUGIC is not known, and would be of interest to enable further interpretation of these results and could inform future clinical practice. This is important in the context that recommended practice, following diagnosis of esophageal strictures, esophageal and gastric ulcers, varies between current clinical guidelines internationally[3, 51]. Patients diagnosed with BE-LGD at baseline represent a high risk group for PEEN. This observation is consistent with both the high prevalence of HGD/EAC in patients with LGD and the known inverse association between neoplasia detection rate (the proportion with BE diagnosed with HGD/EAC at index surveillance endoscopy) and PEEN diagnosed within one year of surveillance[52].

This systematic review has a number of strengths. The study protocol was pre-registered, and the systematic search strategy identified 25 studies that included data on 81, 184 UGI cancers, including 7, 926 with PEUGIC. While previous systematic reviews have sought to determine the prevalence of PEUGIC[5, 53], as far as we are aware this is the first to provide a comprehensive and contemporaneous global assessment of the characteristics of PEUGIC in clinically relevant domains, relative to detected cancers, with relevant subgroup analyses; together with estimation of the prevalence of EGD findings preceding diagnosis of PEUGIC. This has provided insights into the epidemiology of PEUGIC, including their aetiology and clinical and endoscopic presentation. We anticipated common insights across indications for EGD which might only become apparent through collective synthesis, in addition to analyses stratified by indication, from which context-specific insights were sought (including unselected (predominantly symptomatic, BE surveillance and gastric cancer screening cohorts). Studies were selected from a range of locations including Europe, the US, and Australasia, and as such the results are broadly generalisable. For key characteristics, including demography, presentation and tumor staging, given large pooled sample sizes, estimates were precise and comparisons were sufficiently powered to detect smaller differences that would not necessarily otherwise be elicited in individual studies. The overall conclusions of this research unchanged following sensitivity analyses which stratified effect sizes according to the intervals used to define PEUGIC. This systematic review has some limitations. The lack of any significant associations between endoscopic/procedural characteristics (high definition endoscope, sedation, an inpatient setting, clinician experience or primary specialty of the endscopist) and PEUGIC should be cautiously interpreted. These associations are based on few studies with relatively small numbers with PEUGIC. They are also unadjusted associations, potentially precluding causal interpretation. Substantial heterogeneity was noted for

many associations in each domain (demographic, clinical, endoscopic/procedural and tumor-related), however this heterogeneity was partly explained by both primary tumor site and EGD indication (diagnostic, surveillance and screening).

This systematic review has implications for clinical practice and future research. Given PEUGIC are common (relative to detected cancers) and that delays in diagnosis are very likely clinically significant, strategies aimed at reducing the rate of PEUGIC and minimizing delays in diagnosis need prioritisation and are urgently required. Such strategies should be underpinned by large, representative epidemiological investigations with PEUGIC as a key outcome. There is a relative paucity of research which compares the clinical and endoscopic characteristics of PEEC in BE populations. The higher rates of PEUGIC in women in the West, disparities in risk with ethnicity and the impact of socioeconomic status also deserves further research. There is a lack of evidence which examines endoscopic quality metrics and procedural factors and PEUGIC. Clinicians should be mindful that patients with PEUGIC less commonly present with alarm symptoms (compared with detected cancers). PEUGIC can occur at any site in the upper tract, however, respectively for PEEC and PEGC there is a slight preponderance for the upper esophagus and gastric body. PEGC commonly occur in the context of intestinal metaplasia and most commonly arises in the gastric body. Meticulous inspection of the UGI tract with detailed mucosal visualization and recognition of subtle malignant abnormalities will likely minimise PEUGIC rates.

In conclusion, based on a meta-analysis of 25 studies, PEUGIC are common (the pooled prevalence of 10.7%) and the mean and median delay in diagnosis is substantial. PEUGIC are more common in women in the Western world. PEUGIC less commonly present with dysphagia and weight loss, likely due to less advanced cancer stage than detected UGI cancers. PEEC are more commonly ultimately diagnosed in the upper esophagus relative to detected tumors, however most are still diagnosed in the mid and lower esophagus. The gastric body is the predilictive site for PEGC. Endoscopic abnormalities reported prior to diagnosis of PEUGIC are very common, however their relative importance (compared with patients not diagnosed with cancer within three years) is not known. Barrett's associated LGD at baseline is a strong risk factor for PEEN. Evidence-based strategies are required to target the prevention of PEUGIC and reduce delays in diagnosis, with the aim of ultimately improving prognosis.

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Figure 1. PRISMA Flow Diagram

Abbreviations: PEUGIC, post-endoscopy upper gastrointestinal cancer
[a]Citation searching did not highlight any studies eligible for inclusion

Figure 2. Meta-analysis of demographic, clinical, endoscopic/procedural and tumour-related characteristics in patients with post-endoscopy versus detected upper gastrointestinal cancers

Abbreviations: EC, esophageal cancer; GC, gastric cancer; n, number; PEUGIC, post-endoscopy upper gastrointestinal cancer; PPI, Proton pump inhibitor
Deprivation measured using Townsend deprivation index in quintiles (3^{rd} – 5^{th} vs. 1-2^{nd})
Charlson comorbidity score (each co-morbidity assigned a weight from 1 – 6).

Figure 3. Meta-analysis of proportions of findings in the "cancer-negative" esophagogastroduodenoscopy preceding diagnosis of PEUGIC

Abbreviations: PEUGIC, post-endoscopy upper gastrointestinal cancer.
Endoscopic findings reported for PEUGIC diagnosed 6-36 months after a "cancer-negative" endoscopy. Site-specific findings reported only.

Table 1. Characteristics of selected studies

CC, Case-control study; DU; duodenal ulcer; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; GU, gastric ulcer; HGD, HGD; IM; intestinal metaplasia; MC, multi-centre; mo, months; NA, not applicable; NDBO, non-dysplastic Barrett's esophagus; NI, Northern Ireland; NR, not reported; PB, population based; PEEN, Post-endoscopy esophageal neoplasia; PEUGIC, post-endoscopy upper gastrointestinal cancer; RC, retrospective cohort; SC, single centre; UK, United Kingdom; US, United States; yrs, years.
Unselected cohorts comprised EGDs performed for a variety of indications (including diagnostic, therapeutic, surveillance and screening); surveillance cohorts were for Barrett's esophagus surveillance; screening cohorts were for gastric cancer screening.
Sex and age presented where available for the PEUGIC group
[a]Median reported where mean not available
[b]In 3 patients with ≥ 3 EGDs with biopsies in the 6 months prior to diagnosis were not considered missed cancers.
[c]Mean reported where median not available
[d]From the date of diagnosis of Barrett's esophagus
[e]applicable to whole cohort with upper gastrointestinal cancer
[f]% male in the PEEN group (HGD/EAC as composite outcome)
[g]in addition status as "missed" based on review of prior endoscopy reports.
[h]Mean age at initial cancer-negative endoscopy

Table 2. Meta-analysis of characteristics of post-endoscopy and initially detected upper gastrointestinal cancers stratified by primary tumor site.

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; n, number; PEEC, post-endoscopy esophageal cancer; PEGC, post-endoscopy gastric cancer; PPI, Proton pump inhibitor.
[a]Effect size expressed as mean difference. All other effect sizes expressed as odds ratios; [b]compared with sessile/mass

What You Need to Know:

BACKGROUND AND CONTEXT

Post-endoscopy upper gastrointestinal (UGI) cancers (PEUGIC) account for 10% of UGI cancers. Their epidemiology is poorly understood.

NEW FINDINGS

The mean delay in diagnosis is 17 months. Such patients less commonly (OR 0.46) present with alarm symptoms than detected cancers. Abnormalities are commonly (>75%) reported in the initial "cancer-negative" endoscopy.

LIMITATIONS

There was substantial heterogeneity among estimates from the different studies. This could be partly accounted for by differences in endoscopy indication, primary tumor site and geographic location.

IMPACT

Improved understanding of the epidemiology of PEUGIC should inform strategies to prevent or minimise the delay in diagnosis.

Short summary

Patients with upper gastrointestinal (GI) cancers which are not initially detected by esophagogastroduodenoscopy (EGD) are less likely to have classical alarm symptoms. Preceding abnormalties on EGD are common.