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Systematic review with meta-analysis: Prevalence of prior and concurrent Barrett's oesophagus in oesophageal adenocarcinoma patients

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Abstract

Background: The proportions of patients with oesophageal adenocarcinoma (OAC) diagnosed by Barrett's oesophagus surveillance or with preexisting Barrett's oesophagus are unclear.

Aim: A systematic review and meta-analysis to estimate the prevalence of prior and concurrent Barrett's oesophagus diagnosis among patients with OAC or oesophagogastric junction adenocarcinomas (OGJAC).

Methods: We searched PubMed and Embase to identify studies published 1966–1/8/2020 that examined the prevalence of prior (≥6 months) or concurrent Barrett's diagnosis (at cancer diagnosis) among OAC and OGJAC patients. Random effects models estimated overall and stratified pooled prevalence rates.

Results: A total of 69 studies, including 33,002 OAC patients (53 studies) and 2,712 with OGJAC (28 studies) were included. The pooled prevalence of prior Barrett's oesophagus diagnosis

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DISCLAIMER

The opinions expressed reflect those of the authors and not necessarily those of the Department of Veterans Affairs, the US government or Baylor College of Medicine.

in OAC was 11.8% (95% confidence interval [CI] 8.4–15.6%). The prevalence of prior Barrett's oesophagus diagnosis was higher in single-center resection studies (16.0%, 95%CI 8.7–24.9%) than population-based cancer registry studies (8.4%, 95%CI 5.5–11.9%). The prevalence of concurrent Barrett's oesophagus in OAC was 56.6% (95%CI 48.5–64.6%). Studies with 100% early stage OAC had higher prevalence of concurrent Barrett's oesophagus (91.3%, 95%CI 82.4–97.6%) than studies with <50% early OAC (39.7%, 95%CI 33.7–45.9%). In OGJAC, the prevalence of prior and concurrent Barrett's oesophagus was 23.2% (95%CI 7.5–44.0%) and 26.3% (95%CI 17.8–35.7%), respectively.

Conclusions: Most patients with OAC have Barrett's oesophagus. Our meta-analysis found ~12% of OAC patients had prior Barrett's diagnosis, but concurrent Barrett's oesophagus was found in ~57% at the time of OAC diagnosis. This represents a considerable missed opportunity for Barrett's oesophagus screening.

Keywords

oesophageal adenocarcinoma; Barrett's oesophagus; oesophagogastric junction adenocarcinoma; prevalence; systematic review; meta-analysis

Introduction

Barrett's oesophagus is the only known precursor lesion of oesophageal adenocarcinoma (OAC) [1], a rapidly increasing, highly fatal cancer [2, 3]. Much clinical effort has therefore focused on ongoing surveillance after an index Barrett's oesophagus diagnosis. However, absolute risk of OAC in Barrett's oesophagus without dysplasia is low (0.1–0.5% per year vs. 6% per year in Barrett's oesophagus with high-grade dysplasia [1, 4, 5]), with conflicting evidence as to whether Barrett's oesophagus surveillance reduces OAC-related mortality [6–9].

Furthermore, the vast majority of OAC cases have no prior diagnosis of Barrett's oesophagus at their cancer diagnosis. The size of this gap is best demonstrated in the last meta-analysis to determine the prevalence of prior Barrett's oesophagus diagnosis among resected OAC cases that included studies published from 1966–2000 [10]. Among 12 studies involving 1503 patients with resected OAC, only 4.7% had a prior diagnosis of Barrett's oesophagus. This meta-analysis excluded studies of non-resected OAC cases and therefore did not account for prior diagnosis of Barrett's oesophagus among patients with all stages of OAC. Additionally, it included studies that combined OAC and oesophagogastric junction adenocarcinomas (OGJAC), therefore independent prevalence estimates for OAC and OGJAC were not reported. Evaluating data from more contemporary studies may be more informative regarding prevalence of Barrett's oesophagus in OAC as newer cohorts are more likely to have a prior diagnosis of Barrett's and include early stage OAC patients given increased Barrett's oesophagus screening and surveillance practices following GI societal recommendations in 1998 [11].

Therefore, we conducted a systematic review and meta-analysis of the published literature to estimate the prevalence of prior as well as concurrent Barrett's oesophagus diagnosis among

OAC and OGJAC patients. In addition, we focused on Barrett's oesophagus prevalence within studies published in the past 10 years.

Methods

Search Strategy and Selection Criteria:

We conducted and reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Two authors (MCT, NM) independently searched Pubmed and Embase databases for full, original research studies published in print or online in English from 1966 to January 8, 2020 with the following inclusion criteria: 1) reported number of patients with OAC and/or OGJAC; 2) reported number of patients within the cohort with prior and/or concurrent Barrett's oesophagus diagnosis; and 3) only human studies. We excluded: 1) studies that did not report both numbers of patients with OAC/OGJAC and Barrett's oesophagus; 2) abstracts only; 3) reviews, editorials, letters to the editor; 4) studies with <10 OAC/OGJAC patients due to imprecise prevalence estimates; or 5) studies with OAC/OGJAC cell lines, tissues, or xenografts. The search strategy was conducted by a medical librarian (A.S.), and the details of Medical Subject Headings (MeSH) search are included in Appendix 1. Our search strategy also included ancestry search of bibliographies of all included studies and any relevant systematic reviews to identify additional studies that may have been missed. All studies included by either reviewer underwent a second review to exclude studies with indistinguishably combined OAC/OGJAC cohorts and studies with potentially overlapping populations. For manuscripts with potentially overlapping study populations, only the one with the largest sample size was included. Consensus was reached by both authors (MCT, NM) for final study inclusion.

OAC/OGJAC and Barrett's oesophagus identification:

In studies that specified cancer locations based on Siewert classification [13], Siewert I tumors (midpoint 1cm to 5cm proximal to anatomic OGJ) were included with OAC, while Siewert II (midpoint 1cm proximal to 2cm distal to anatomic OGJ) were included with OGJAC. Siewert III and cardia cancers were excluded. Early stage OAC/OGJAC, or those amenable to resection, were defined as T1, T2 or stage 1 or 2 cancers. Prior Barrett's oesophagus was defined as diagnosed ≥6 months prior to OAC/OGJAC diagnosis, when specified. We defined concurrent Barrett's oesophagus as Barrett's found on histopathology at the time of cancer diagnosis. Studies that reported numbers with Barrett's oesophagus at the time of cancer diagnosis but did not specify how many of these were diagnosed prior to cancer diagnosis were classified as concurrent Barrett's oesophagus to reduce misclassification of prior Barrett's oesophagus diagnosis. We included studies that defined Barrett's oesophagus as "specialized intestinal epithelium", "intestinal metaplasia", "columnar epithelium", or endoscopic appearance of Barrett's oesophagus.

Data Abstraction and Quality Assessment:

Two authors (MCT, NM) independently abstracted data from included studies including: study characteristics (i.e., study design, location, study period, study site, and study population), patient clinical and sociodemographic characteristics (i.e., method of OAC/

OGJAC determination, Barrett's oesophagus determination, Siewert classification, mean age, percent male, percent White, and percent diagnosed with early stage OAC/OGJAC), number of patients with OAC/OGJAC, number of patients with Barrett's oesophagus, and assessment of study quality. If a subgroup of the study was included in our review but demographics were only reported for the whole population, we included the reported mean age and percent males.

Assessment of study quality was modified from the "The Joanna Briggs Institute Prevalence Critical Appraisal Tool", which is a validated critical appraisal tool for systematic reviews addressing questions of prevalence [14]. Two authors independently assessed sample representation, participant recruitment, sample size, cohort descriptions, standardized measurement of Barrett's oesophagus and OAC/OGJAC, reliable measurement, confounding factors, and subpopulation identification. Studies were determined to have adequately identified sub-populations if they included data on number of early stage cancers and type of study as these were the stratified analysis conducted. Discordance in data abstraction or quality assessment were resolved by consensus agreement by both abstractors.

Statistical Analysis:

We used random effects analysis to estimate pooled prevalence rates of prior and concurrent Barrett's oesophagus diagnosis among OAC and of OGJAC patients along with their 95% confidence intervals (CI). For studies that did not report prevalence of Barrett's oesophagus, we calculated the prevalence based on reported numbers of OAC/OGJAC and Barrett's oesophagus. We used recommended Tukey Freeman arcsine transformed proportion and variance estimates for meta-analytic calculations of prevalence data [15], with results presented as forest plots. Between-study heterogeneity was assessed using the Higgins inconsistency index (I^2), and I^2>50% was considered substantial heterogeneity [16]. To assess for potential small study or publication bias, we used Egger's and graphically by evaluating asymmetry in funnel plots of the Tukey Freeman arcsine transformed proportion versus its standard error. We also assessed secular trends in pooled estimate over time meta-analyses.

We also performed *a priori* specified stratified subgroup and sensitivity analyses to better qualify our findings on overall association between prior and concurrent Barrett's oesophagus and OAC/OGJAC and to identify factors related to design that contributed to any observed between-study (non-random) variation. These included meta-analyses to obtain pooled prevalence for specified sub-groups based on study site (single-center, multi-center, population-based), location (U.S./Canada, Europe/Australia, Asia, other), method of OAC determination (resection only, biopsy/surgical pathology, database/diagnosis code), sample size (<100, 100–1000, >1000), male proportion (in tertiles), and proportion of early cancers (<50%, 50–99%, 100%). We also assessed if any of these factors was a significant contributor to between-study heterogeneity using univariable meta-regression when there were a minimum 10 studies.

Finally, we performed sensitivity analyses including: 1) restriction to studies published in the last 10 years, and 2) replacing two large, population-based U.S. studies reporting patients from the Surveillance, Epidemiology, and End Results (SEER) [17] and American College

of Surgeons (ACS) databases [18] with 11 additional US studies that were initially excluded due to potentially overlapping study populations as the SEER and ACS database studies.

We performed main meta-analyses including pooled estimates, forest plots, I^2 and related sub-group analyses using the metafor package implemented in Stata version 14 (StataCorp, College Station, TX) and used OpenMEE (http://www.cebm.brown.edu/openmee/) [19], which stores Tukey Freeman arcsine transformed proportion and variance estimates, for performance of remaining analyses, including meta-regression. All reported p-values are two-sided with $p<0.05$ indicating statistical significance.

Results

We identified and reviewed 5,057 potentially relevant studies. Of these, 180 studies were included by at least 1 reviewer for a second review. We excluded 117 studies on second review, including 26 that did not meet inclusion criteria, 26 that reported combined OAC/OGJAC numbers, and 63 with potentially overlapping study populations (of which 11 US studies were used in a sensitivity analysis) (Figure 1).

A total of 69 studies met the eligibility criteria and included 33,002 patients with OAC from 53 studies and 2,712 with OGJAC from 28 studies. These studies were published from 1978 to 2019 and were conducted in U.S./Canada (n=25, 36.2%) [17, 18, 20–42], Europe (n=30, 43.5%) [43–72], Asia (n=11, 15.9%) [73–83], Africa (n=1, 1.4%) [84], South America (n=1, 1.4%) [85], or Australia (n=1, 1.4%) [86] and included 55 single-center (79.7%), 7 multi-center (10.1%), and 7 population-based studies (10.1%) (Tables 1, 2). OAC and OGJAC determination was made using surgical or endoscopic specimens (n=59 studies), diagnosis codes (n=3 studies), or cancer registry (n=7 studies). In 15 studies of prior Barrett's oesophagus diagnosis prevalence, previous Barrett's oesophagus diagnosis determination was made using histopathology (n=5 studies), Barrett's oesophagus registry/database/history (n=5 studies), diagnosis codes (n=2 study), a combination of methods (n=1), or using methods that were not reported (n=2 studies). In 59 studies that reported concurrent Barrett's oesophagus diagnosis prevalence, concurrent Barrett's oesophagus determination was made using histopathology (n=53 studies), Barrett's registry/database (n=1 study), survey (n=1 study), a combination of methods (n=1), or was not reported (n=3 studies). Demographic and clinical characteristics of the included studies are shown in Supplementary Table 1.

Evaluation of Studies for Risk of Bias

Risk of bias assessments for the 69 included studies are shown in Supplementary Table 2. Overall, only 10 of 69 studies included a representative sample of the target population, enrolled consecutive patients, had adequate sample size, and reliably measured OAC/OGJAC and Barrett's oesophagus using objective criteria [18, 23, 24, 46–49, 53, 63, 73]. Few studies fully described the characteristics of OAC/OGJAC patients (n=10), but most studies did not clearly state that consecutive patients were included (n=44) or reliably measure both OAC/OGJAC and Barrett's oesophagus using histopathology and intestinal metaplasia or goblet cells as standard criteria (n=41). All studies had adequate sample size as we excluded studies with <10 OAC/OGJAC patients. Twenty-nine studies had a representative sample of OAC/OGJAC patients (i.e., included all cancer stages). Most

studies included cancer stage data allowing stratified subgroup analysis based on percent early cancers (n=48).

Pooled Prevalence of Barrett's oesophagus in OAC

Among 11 studies including 25,248 patients with OAC, the pooled prevalence of prior Barrett's oesophagus diagnosis was 11.8% (95% CI 8.4–15.6%; I^2=98%) (Figure 2). Three studies defined prior Barrett's oesophagus diagnosis as that was diagnosed ≥6 months prior to cancer diagnosis [17, 42, 44] but did not specify the number of Barrett's oesophagus detected within 12 months; one study defined prior Barrett's oesophagus as that diagnosed ≥12 months prior to cancer diagnosis [63], and the rest did not specify time interval for defining prior Barrett's oesophagus. The pooled prevalence of prior Barrett's oesophagus among 814 OAC patients was higher in the 6 single-center studies, including mostly surgical resections (16.0%, 95% CI 8.7–24.9%; I^2=83%) than among the 24,434 OAC patients in the 5 population-based cancer registry studies (8.4%, 95% CI 5.5–11.9%; I^2=98%) (heterogeneity between groups p=0.05). Of 5 studies that specify patients who received Barrett's oesophagus surveillance endoscopy [51, 57, 63, 65, 68], the prevalence of OAC patients that were diagnosed based on Barrett's oesophagus surveillance endoscopy was 11.6% (95% CI 4.0–22.1%).

In 45 studies of 7,926 OAC patients, the prevalence of concurrent Barrett's oesophagus was 56.6% (95% CI 48.5–64.6%; I^2=98%). Stratified meta-analyses showed numerically lower prevalence of concurrent Barrett's oesophagus among population based studies (3 studies; 2,402 OAC patients; prevalence=43.0%, 95% CI 26.5–60.4%; I^2 not calculated) than single-center studies (39 studies; 5,121 OAC patients; prevalence=58.3%, 95% CI 47.5–68.6%; I^2=98%) and multi-center studies (5 studies; 403 OAC patients; prevalence=54.7%, 95% CI 34.8–73.8%; I^2=91%); however, the test for heterogeneity between these three sub-groups was not statistically significant (p=0.35) (Figure 3). When evaluating the association between cancer stage and prevalence of concurrent Barrett's oesophagus, we found that in 10 studies (451 OAC patients) with 100% early stage cancers, the pooled prevalence of concurrent Barrett's oesophagus was higher (91.3%, 95% CI 82.4–97.6%; I^2=86%) than in 7 studies (1,011 OAC patients) with 50–99% of the cohort with early stage cancers (43.8%, 95% CI 12.2–78.4%; I^2=99%) and 13 studies (3,616 OAC patients) with <50% of the cohort with early stage cancers (39.7%, 95% CI 33.7–45.9%; I^2=89%) (p<0.001) (Figure 4).

Sensitivity analyses

Meta-analysis restricted to studies published in the last 10 years of the review (2010–2020) showed pooled prevalence of prior Barrett's oesophagus was 11.8% (95% CI 8.2–16.0, I^2=98%) (8 studies; 25,120 OAC patients) and the pooled prevalence of concurrent Barrett's oesophagus was 56.2% (95% CI 42.0–69.9%, I^2=98%) (18 studies; 3,520 OAC patients), which was not different from the overall prevalence (Figure not shown).

We conducted a sensitivity analysis excluding the two large US population-based cohorts [17, 18] and replaced them with 11 US studies with potentially overlapping study populations that were excluded in the primary analysis (Supplementary Table 3) [87–97]. The pooled prevalence of prior Barrett's oesophagus among 14 studies including 20,891

OAC patients was 11.4% (95% CI 8.3–14.8%; I^2=96%) (Supplementary Figure 1). The prevalence of concurrent Barrett's oesophagus among 6,867 OAC patients in 53 studies was 53.4% (95% CI 45.5–61.1%; I^2=97%) (Supplementary Figure 2). Both estimates were similar to the pooled prevalence of prior Barrett's oesophagus diagnosis in the primary analysis.

Bias and heterogeneity assessments

Graphical funnel plot and Egger's test demonstrated significant small study bias (p<0.001); although pooled meta-analytic estimates of studies stratified by sample size (<100, 100–1000, >1000 OAC cases) demonstrated only modest differences in pooled prevalence estimates (Figure 5). Among the other variables examined as potential factors explaining observed between-study heterogeneity in univariable meta-regression, method of OAC determination (resection only, biopsy/surgical pathology, database/diagnosis code) and proportion of early cancers (categorically <50%, 50–99%, 100%) were significant predictors (p=0.03 and <0.001, respectively) (Supplementary Table 4).

In the cumulative meta-analysis where we examined how the observed pooled estimate changed with studies subsequently added over time, the cumulative pooled prevalence was initially much higher based on studies published prior to 1990, then attenuated with addition of studies published in the 1990s, and largely stabilized by 2000 onwards (Supplementary Figure 3).

Pooled Prevalence of Barrett's oesophagus in OGJAC

Our primary analysis included 6 studies with 664 patients with OGJAC and found a pooled prevalence of prior Barrett's oesophagus diagnosis of 23.2% (95% CI 7.5–44.0%; I^2=97%) (Supplementary Figure 4). The pooled prevalence of prior Barrett's oesophagus was higher in the 5 single-center OGJAC studies (29.3%, 95% CI: 13.1–48.8%) compared with the 1 population-based study (2.6%, 95% CI: 1.0–6.5%) (p<0.001). In 25 studies of 2,352 OGJAC patients, the pooled prevalence of concurrent Barrett's oesophagus was 26.3% (95% CI 17.8–35.7%; I^2=95%) (Supplementary Figure 5). The pooled prevalence of concurrent Barrett's oesophagus among OGJAC patients was no different in the 20 single-center studies (28.1%, 95% CI: 17.1–40.5%) as the 4 multi-center (22.3%, 95% CI: 12.0–34.7%) and 1 population-based study (15.6%, 95% CI: 10.7–22.1%) (p=0.11). Given limited number of studies, we did not perform the Egger's test or meta-regression for OGJAC studies.

Discussion

Among patients with OAC, prior Barrett's oesophagus diagnosis was present in 11.8%, while 56.6% had concurrent Barrett's oesophagus diagnosed at the time of OAC. Studies that included all early stage OAC patients had a higher prevalence of concurrent Barrett's oesophagus (91.3%) than studies that included all stages of OAC (39.7%). Among those with OGJAC, the pooled prevalence of prior Barrett's oesophagus diagnosis was 23.2%, and concurrent Barrett's oesophagus was 26.3%.

Our study reported a higher prevalence of prior Barrett's oesophagus diagnosis than the one previous meta-analysis (4.7% ± 2.9%) of studies published through 2000 [10]. The previous

meta-analysis included 12 studies comprising 1503 cases of OAC/OGJAC but included studies that combined OAC with high-grade dysplasia, gastric cardia and OGJAC (5 studies), which may account for the smaller Barrett's oesophagus prevalence compared to our meta-analysis. We excluded 6 of these studies from our analysis (5 indistinguishably combined OAC and OGJAC, 1 with overlapping population as another included study). We found a similar prevalence of prior Barrett's oesophagus diagnosis (11.8%) when pooling contemporary studies published in the last 10 years, although these studies included cohorts as far back as 1980, so likely did not reflect the most contemporary practice patterns. We were unable to restrict to solely contemporary cohorts as none of the studies reporting prior Barrett's oesophagus diagnosis were limited to cohorts from the last 10 years.

The low prevalence of previously known Barrett's oesophagus diagnosis among OAC patients likely reflects missed screening opportunities in patients who did in fact have underlying Barrett's oesophagus. It is possible but less likely that these patients did not have any of the known demographic or clinical Barrett's oesophagus risk factors (reflux symptoms, obesity, age >50, male, Caucasians, family history of esophageal cancer). Detailed data on Barrett's oesophagus risk factors were not reported in the studies, and 15.9% of studies reported racial breakdown. We did not estimate prevalence of prior endoscopy in this meta-analysis but previous studies suggest Barrett's oesophagus is under-diagnosed prior to OAC due to lack of endoscopic screening. Our previous study of 182 patients with OAC reported only 24.7% underwent any pre-OAC diagnosis endoscopy, and of those who did not undergo previous endoscopy, most had risk factors for Barrett's oesophagus or OAC (63.5%) [98]. When we pooled studies that confirmed the concurrent presence of Barrett's oesophagus on histopathology at the time of cancer diagnosis, we found a much higher prevalence of Barrett's oesophagus, indicating that the majority of OAC patients have underlying Barrett's oesophagus that was not previously diagnosed. We further examined studies that included only early stage OAC and found the pooled prevalence of concurrent Barrett's oesophagus was much higher (91.3%) compared to studies with all stages of OAC (39.7%). This finding strongly supports that advanced OAC likely overgrows the underlying Barrett's oesophagus making Barrett's detection easier in earlier stages [99]. A second explanation to account for the considerable proportion of OAC patients without Barrett's oesophagus at the time of OAC diagnosis (60.3% in studies with all OAC stages) may be a mechanism of OAC development that excludes Barrett's oesophagus. A recent study found improved survival in OAC patients with synchronous Barrett's oesophagus compared to those without Barrett's oesophagus after adjusting for cancer stage, proposing the possibility of a different phenotype of OAC development [8].

We found 23.2% of those with OGJAC had a prior Barrett's oesophagus diagnosis and 26.3% had Barrett's oesophagus confirmed on histopathology at the time of cancer diagnosis; this estimate has not previously been reported. OGJAC shares several risk factors with OAC (e.g., reflux, obesity) [100]. OGJAC are classified by location using the Siewert classification [13]. Siewert type I and II are treated similarly to OAC, while Siewert III and cardia cancers are treated following gastric cancer protocols [50, 101]. We included Siewert I OGJAC with OAC, and Siewert II cancers with OGJAC [13]. Our findings confirm that Siewert II OGJAC occurs sometimes in the setting of Barrett's oesophagus, and some OGJAC may follow the same carcinoma sequence and share the same risk factors as

Barrett's oesophagus. However, Barrett's oesophagus was found at the time of cancer diagnosis less commonly in OGJAC than in OAC, which may point to a different mechanism of OGJAC pathogenesis apart from Barrett's oesophagus in some cases of OGJAC.

Our meta-analysis has multiple strengths including structured comprehensive search strategy resulting in >5000 reviewed studies by 2 reviewers, use of ancestry/bibliography searches to identify any missed studies, contacting study authors for unpublished data, and defining prior and concurrent Barrett's oesophagus diagnosis, OAC, and OGJAC *a priori*. We employed a methodologically rigorous approach including sub-group analysis by study site and proportion of early cancers and sensitivity analyses restricted to contemporary studies from the last 10 years and replacing 2 large US population-based studies with 11 excluded US single-center studies. Additionally, we used multiple methods including meta-regression and cumulative meta-analysis to identify potential sources of between-study heterogeneity and bias.

Our meta-analysis has several limitations. There were no studies that were prospectively conducted with the aim of evaluating Barrett's oesophagus prevalence among OAC/OGJAC patients, thus systematic evaluation for Barrett's oesophagus was lacking across studies. Especially among studies that define Barrett's oesophagus using registry or databases, the prevalence of Barrett's oesophagus may have been under-estimated as it was not systematically captured at the time of cancer diagnosis. The definitions of Barrett's oesophagus, OAC, OGJAC varied across studies in completeness. Only 3 studies specified prior Barrett's oesophagus diagnosis as >6 months [17, 42, 44] and 1 additional study as >12 months [63] prior to cancer diagnosis. In order to reduce misclassification of prior Barrett's oesophagus diagnosis cases, we classified cases as concurrent Barrett's oesophagus diagnosis when studies did not specifically state that there was a prior diagnosis or that cancer was found on Barrett's oesophagus surveillance endoscopy; therefore, in the studies without mention of timing of Barrett's oesophagus diagnosis, cases of prior Barrett's oesophagus and concurrent Barrett's oesophagus may have been misclassified. There was also poor reporting on race/ethnicity and consecutiveness of study population. The overall sample size was relatively small, including those with prior Barrett's oesophagus diagnosis in OAC and OGJAC. Additionally, significant heterogeneity was seen among the reported pooled prevalence. Meta-regression analyses demonstrated that variable proportion of early OAC accounted for some of this heterogeneity, and stratified meta-analysis by proportion of early OAC decreased the heterogeneity seen in the overall pooled prevalence. The significant small study bias is likely substantially explained by the relation of sample size to method of OAC determination, as smaller studies tended to determine OAC on resection specimens and larger studies on registry/diagnosis codes.

Overall, although up to 91% of all newly diagnosed early stage OAC patients had Barrett's oesophagus seen on histopathology at the time of cancer diagnosis, the prevalence of known Barrett's oesophagus prior to OAC diagnosis remains low among these patients. These findings call for increased use of Barrett's oesophagus screening protocols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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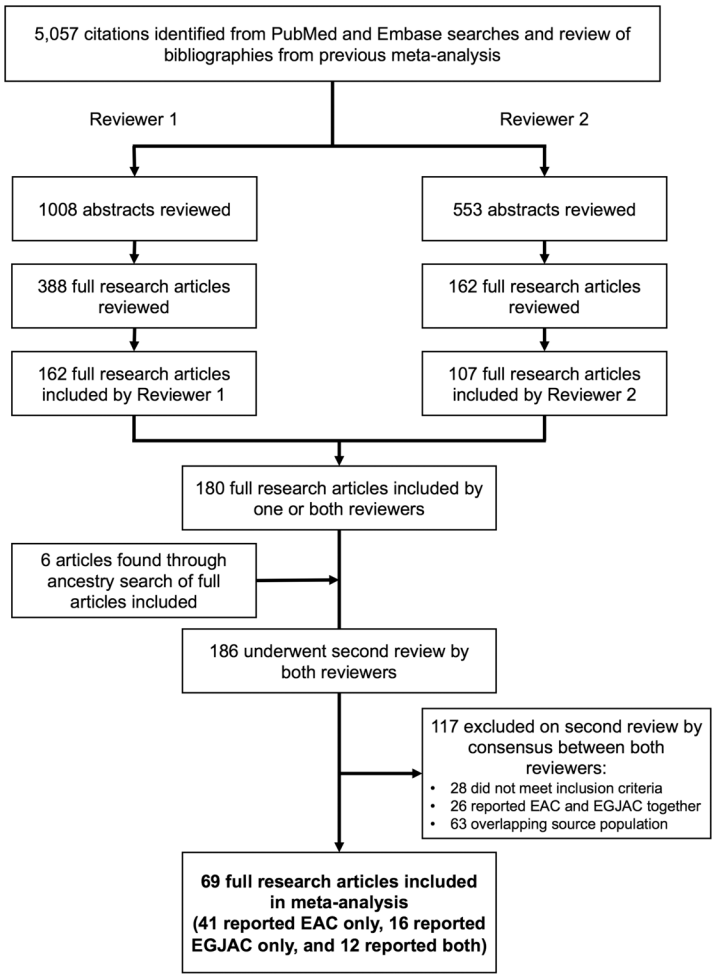

Figure 1.
Study flow diagram.

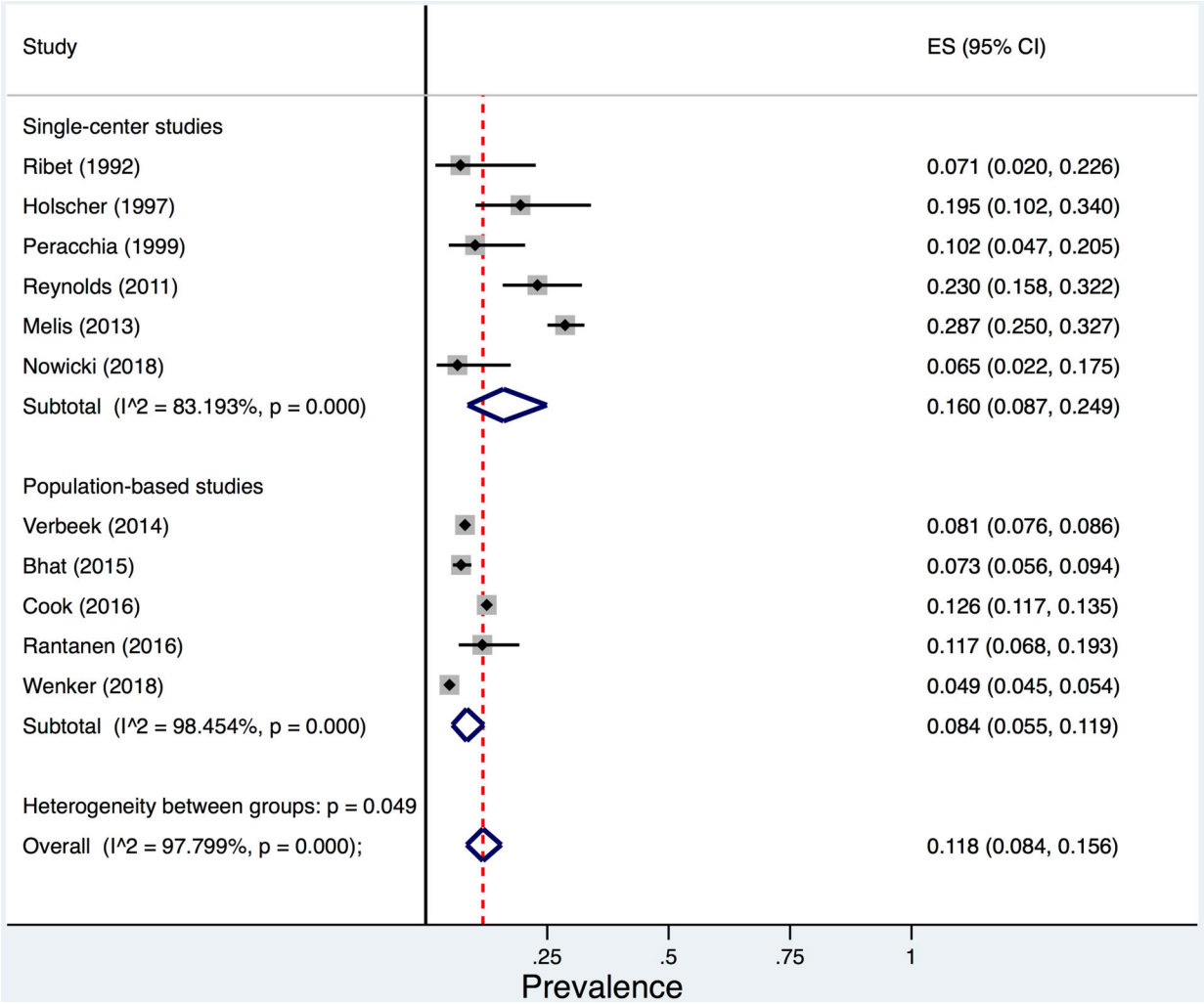

Figure 2.
Pooled prevalence of prior Barrett's oesophagus diagnosis among 25,248 oesophageal adenocarcinoma patients from 11 studies.

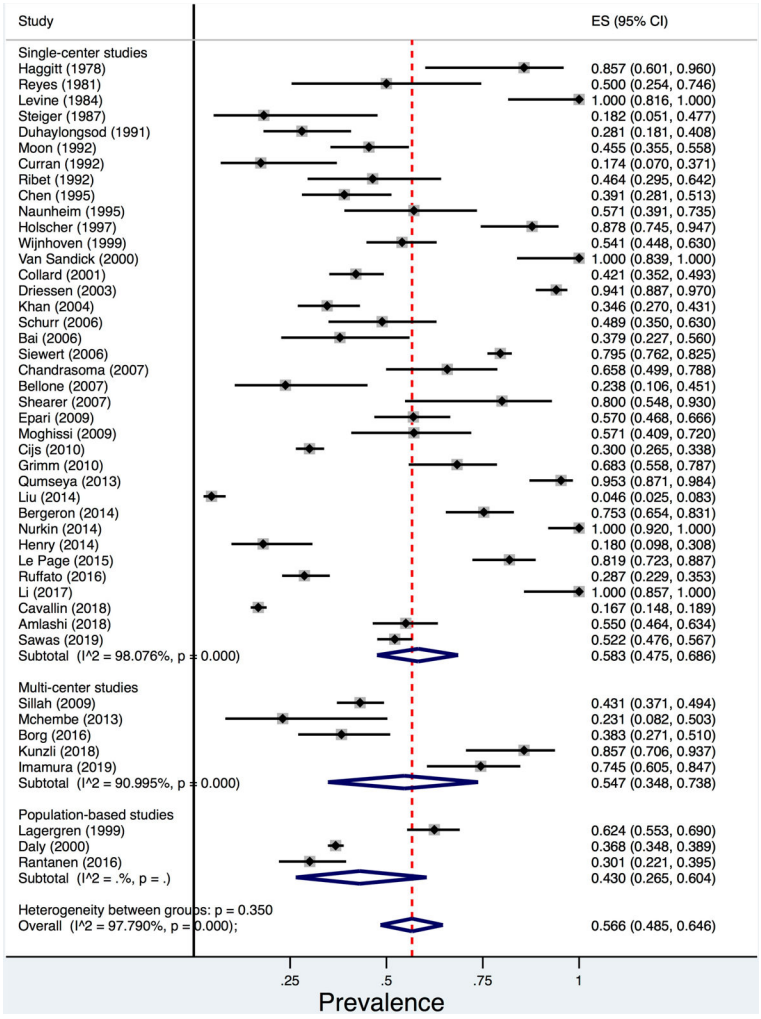

Figure 3.

Pooled prevalence of concurrent Barrett's oesophagus diagnosis among 7,926 oesophageal adenocarcinoma patients from 45 studies.

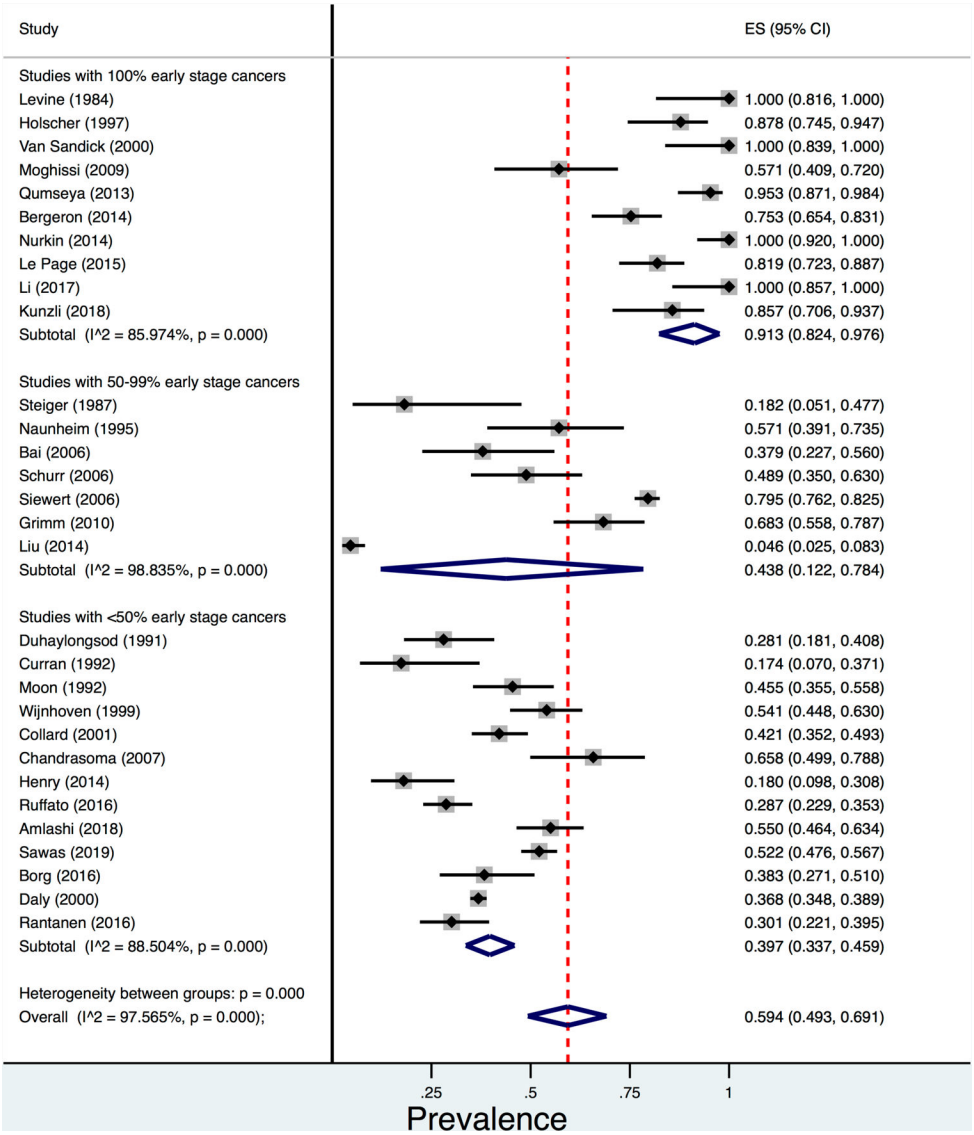

Figure 4.

Pooled prevalence of concurrent Barrett's oesophagus diagnosis among oesophageal adenocarcinoma (OAC) patients comparing 10 studies (451 OAC patients) with 100% early stage cancers to 7 studies (1,011 OAC patients) with 50–99% early stage cancers and 13 studies (3,616 OAC patients) with <50% early stage cancers.

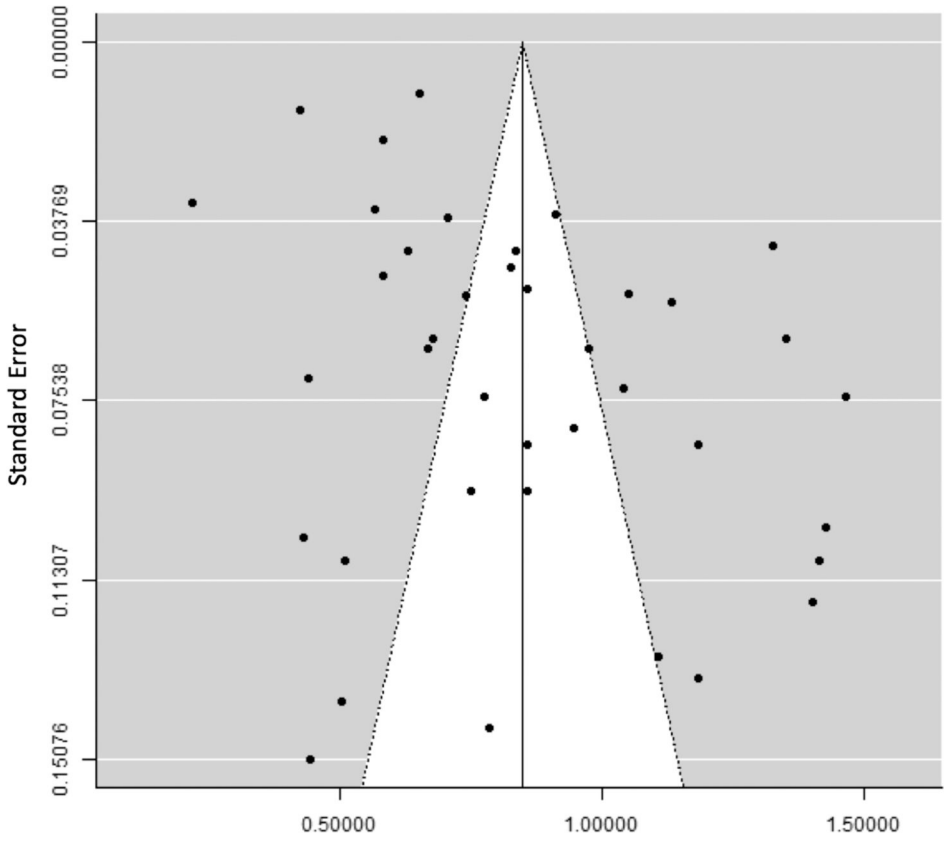

Figure 5.
Funnel plot showing significant small study bias among 45 studies evaluating prevalence of concurrent Barrett's oesophagus diagnosis among 7,926 oesophageal adenocarcinoma patients.

Table 1.

Study characteristics of 53 studies of 33,002 oesophageal adenocarcinoma (OAC) patients.

Ref	Author	Year	Study Design	Study Location	Study Period	OAC determination	Barrett's Oesophagus determination	# Total OAC	# Prior BE Diagnosis	# Concurrent BE
Single-center Studies										
[40]	Amlashi	2018	cross-sectional	Houston, Texas	2002–2015	hospital cancer registry of patients after chemoradiation therapy	pathology	129		71
[73]	Bai	2006	cross-sectional	Xian, China	1/1995–12/1999	pathology reports (biopsy, surgical resection)	pathology (biopsy or surgery)	29		11
[43]	Bellone	2007	case series	Turin, Italy	1/2002–12/2005	surgical resection pathology	pathology	21		5
[20]	Bergeron	2014	case series	Ann Arbor, Michigan	7/2005–7/2011	surgical resection pathology (only Tis or T1 cancers)	pathology	89		67
[45]	Cavallin	2018	cohort	Padova, Italy	1/1980–12/2011	hospital database	hospital database	1243		208
[41]	Chandrasoma	2007	case series	Los Angeles, California	1997–2000	surgical resection pathology	pathology	38		25
[22]	Chen	1995	case series	Winston-Salem, North Carolina	1975–1992	hospital cancer registry	pathology (biopsy or surgery)	64		25
[46]	Cijs	2010	cohort	Rotterdam, Netherlands	1/1985–1/2005	surgical resection pathology	pathology	596		179
[47]	Collard	2001	cohort	Brussels, Belgium	11/1984–1/2000	surgical resection pathology	pathology	183		77
[48]	Curran	1992	case series	Galway, Ireland	NR	surgical resection pathology	pathology	23		4
[49]	Driessen	2003	cross-sectional	Leuven, Belgium	1993–2000	surgical resection pathology	pathology (biopsy or surgery)	135		127
[24]	Duhaylongsod	1991	cross-sectional	Durham, North Carolina	1985–1990	surgical resection pathology	pathology	57		16
[86]	Epari	2009	case series	Melbourne, Australia	5/1993–5/2006	surgical resection pathology	pathology (biopsy or surgery)	93		53
[67]	Grimm	2010	case series	Wuerzburg, Germany	1/2001–6/2004	surgical resection pathology	pathology	60		41
[51]	Holscher	1997	cohort	Cologne, Germany	1982–1995	surgical resection pathology	BE surveillance, pathology (EGD or surgery)	41	8	36

Ref	Author	Year	Study Design	Study Location	Study Period	OAC determination	Barrett's Oesophagus determination	# Total OAC	# Prior BE Diagnosis	# Concurrent BE
[26]	Haggitt	1978	case series	Boston, Massachusetts	1927–1976	surgical resection pathology	pathology	14		12
[85]	Henry	2014	cross-sectional	Botucatu, Brazil	2007–2012	pathology	NR	50		9
[52]	Khan	2004	cohort	Nottingham, UK	1987–2001	surgical resection pathology	pathology	130		45
[54]	Le Page	2015	cross-sectional	Edinburgh, UK	2005–2013	endoscopic or surgical resection pathology	pathology	83		68
[38]	Levine	1984	case series	Philadelphia, Pennsylvania	1979–1982	hospital pathology records	pathology	17		17
[29]	Li	2017	case series	Halifax, Canada	2005–2013	endoscopic or surgical resection pathology (only T1 cancers)	pathology	23		23
[76]	Liu	2014	case series	Henan, China	2002–2011	pathology; surgical resection pathology	pathology	217		10
[37]	Melis	2013	case series	Tampa, Florida	6/1994–1/2011	oesophageal cancer database of surgical resections	history of BE	540	155	
[55]	Moghissi	2009	case series	East Yorkshire, UK	1997–2009	pathology (only intramucosal cancers)	pathology	35		20
[30]	Moon	1992	cross-sectional	Milwaukee, Wisconsin	1974–1990	surgical resection pathology	pathology	88		40
[31]	Naunheim	1995	case series	St. Louis, Missouri	1986–1993	pathology (cancers treated with neoadjuvant chemotherapy)	pathology	28		16
[68]	Nowicki	2018	case series	Bydgoszcz, Poland	2004–2014	hospital endoscopy database	BE surveillance	46	3	
[32]	Nurkin	2014	case series	Buffalo, New York	2001–2012	endoscopic resection pathology	pathology	44		44
[65]	Peracchia	1999	case series	Milan, Italy	11/1992–5/1998	surgical resection pathology	BE surveillance	59	6	
[34]	Qumseya	2013	case series	Jacksonville, Florida	2003–2010	endoscopic resection pathology	pathology	64		61
[35]	Reyes	1981	case series	Hines, Illinois	1953–1979	surgical resection pathology	pathology	12		6
[57]	Reynolds	2011	case series	Dublin, Ireland	2004–2008	pathology from database	BE surveillance	100	23	
[66]	Ribet	1992	cross-sectional	Lille Cedex, France	1970–1988	surgical resection pathology	pathology	28	2	13

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Ref	Author	Year	Study Design	Study Location	Study Period	OAC determination	Barrett's Oesophagus determination	# Total OAC	# Prior BE Diagnosis	# Concurrent BE
[69]	Ruffato	2016	case series	Bologna, Italy	2001–2013	surgical resection pathology	pathology	202		58
[39]	Sawas	2019	cohort	Rochester, Minnesota	1996–1997, 2009–2012	hospital database	endoscopy and/or pathology	462		241
[59]	Schurr	2006	case series	Hamburg, Germany	NR	surgical resection pathology	pathology	45		22
[60]	Shearer	2007	cross-sectional	Glasgow, UK	1995–2000	surgical resection pathology	pathology	15		12
[70]	Siewert	2006	cohort	Munich, Germany	7/1982–12/2005	surgical resection pathology	pathology	621		494
[36]	Steiger	1987	case series	Allen Park, Michigan	1975–1982	surgical resection pathology	pathology	11		2
[62]	Van Sandick	2000	case series	Amsterdam, Netherlands	1/1993–1/1998	surgical resection pathology (only pT1 cancers)	pathology	20		20
[64]	Wijnhoven	1999	cross-sectional	Rotterdam, Netherlands	1987–1997	surgical resection pathology	pathology	111		60
Multi-center Studies										
[72]	Borg	2016	case series	Lund & Malmo, Sweden	1/2006–12/2010	surgical resection pathology	pathology	60		23
[81]	Imamura	2019	case series	Tokyo, Kumamoto, Fukuoka, Japan	2006–2013	surgical resection pathology	pathology	47		35
[71]	Kunzli	2018	case series	Amsterdam & Nieuwegein, Netherlands	1/2012–8/2016	endoscopic resection pathology	pathology	35		30
[84]	Mchembe	2013	case series	Bugando, Tanzania	2008–2013	pathology	pathology	13		3
[61]	Sillah	2009	cross-sectional	Manchester, UK	2004–2007	surgical resection pathology	NR	248		107
Population-based Studies										
[44]	Bhat	2015	cross-sectional	Northern Ireland	2003–2008	Northern Ireland Cancer Registry	Northern Ireland Barrett's Oesophagus Register >6 months prior to OAC	716	52	
[102]	Cook	2016	case-control	USA (SEER-Medicare)	1994–2009	SEER-Medicare Cancer Registry (based on ICD9/10 codes)	ICD 9/10 code >6 months prior to OAC diagnosis	5271	662	
[18]	Daly	2000	case series	USA (National Cancer Database)	1/1994–12/1994	National Cancer Database-American College of	survey	2110		777

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Ref	Author	Year	Study Design	Study Location	Study Period	OAC determination	Barrett's Oesophagus determination	# Total OAC	# Prior BE Diagnosis	# Concurrent BE
						Surgeons (based on ICD codes)				
[53]	Lagergren	1999	case-control	Sweden	1994–1997	pathology	pathology	189		118
[56]	Rantanen	2016	case series	Finland	1980–2007	EGD/surgical resection pathology	pathology (biopsy or surgery)	103	12	31
[63]	Verbeek	2014	cross-sectional	Netherlands	1999–2009	Netherlands Cancer Registry	Dutch Pathology Registry	9780	791	
[42]	Wenker	2018	cross-sectional	USA (National VA Database)	2002–2016	VA Cancer Registry (based on ICD codes)	ICD 9 code >6 months prior to OAC diagnosis	8564	419	

BE: Barrett's oesophagus; NR: not reported; EGD: esophagogastroduodenoscopy

Table 2.

Study characteristics of 28 studies of 2,712 oesophagogastric junction adenocarcinomas (OGJAC) patients.

Ref	Author	Year	Study Design	Study Location	Study Period	OGJAC determination	Barrett's oesophagus determination	OGJAC definition	# Total OGJAC	# Prior BE Diagnosis	# Concurrent BE
Single-center Studies											
[40]	Amlashi	2018	cross-sectional	Houston, Texas	2002–2015	hospital cancer registry of patients after chemoradiation therapy	pathology	Siewert 2	98		26
[73]	Bai	2006	cross-sectional	Xian, China	1/1995–12/1999	pathology reports (biopsy, surgical resection)	pathology (biopsy or surgery)	Siewert 2	80		5
[21]	Cameron	2002	case-control	Rochester, Minnesota	1/1996–12/1999	endoscopic or surgical resection pathology (only cancers <2cm)	pathology	within 2 cm of OGJ	22		7
[23]	Demicco	2011	case series	Boston, Massachusetts	1/2000–5/2008	surgical resection pathology	pathology (biopsy or surgery)	Siewert 2	106	19	64
[50]	Fein	1998	case series	Wuerzburg, Germany	1992–1997	surgical resection pathology	pathology	Siewert 2	30		1
[25]	Gaca	2006	cross-sectional	Durham, North Carolina	7/1992–2/2001	surgical resection pathology	NR	within 5cm of OGJ	96	42	
[83]	Gupta	2001	case series	Chandigarh, India	1989–1994	surgical resection pathology	NR	at or extending 2cm distal to OGJ	28		0
[74]	Horii	2011	case-control	Sendai, Japan	2000–2009	pathology (cancers limited to submucosa)	pathology	within 2cm of OGJ and midpoint on oesophageal side	46		23
[82]	Imai	2013	case series	Shizuoka, Japan	9/2002–3/2009	endoscopic resection pathology	pathology	Siewert 2	49		7
[75]	Kamada	2012	cross-sectional	Kurashiki, Japan	1/2001–12/2008	endoscopic or surgical resection pathology	pathology	Siewert 2	80		6
[27]	Karl	2000	cross-sectional	Tampa, Florida	1989–1999	surgical resection pathology	pathology	NR	115		56
[28]	Lada	2013	cohort	Rochester, New York	2000–2011	surgical resection pathology	medical record review, EGD, pathology	NR	211	73	

Ref	Author	Year	Study Design	Study Location	Study Period	OGJAC determination	Barrett's oesophagus determination	OGJAC definition	# Total OGJAC	# Prior BE Diagnosis	# Concurrent BE
[77]	Nagami	2014	cross-sectional	Osaka, Japan	2007–2011	endoscopic dissection pathology	pathology	Siewert 2	43		14
[33]	Pera	1993	cross-sectional	Rochester, Minnesota	1974–1989	pathology	pathology	extending across OGJ	14		5
[57]	Reynolds	2011	cohort	Dublin, Ireland	2004–2008	pathology from database	NR	Siewert 2	53	1	
[58]	Saha	2009	case-control	West Yorkshire, UK	1/2000–12/2006	surgical resection pathology (only pT1 cancers)	pathology	Siewert 2	44	28	31
[39]	Sawas	2019	cohort	Rochester, Minnesota	1996–1997, 2009–2012	hospital database	endoscopy and/or pathology	Siewert 2	288		140
[59]	Schurr	2006	prospective case series	Hamburg, Germany	NR	surgical resection pathology	pathology	Siewert 2	40		5
[60]	Shearer	2007	prospective case series	Glasgow, UK	1995–2000	surgical resection pathology	pathology	Siewert 2	26		13
[70]	Siewert	2006	cohort	Munich, Germany	7/1982–12/2005	surgical resection pathology	pathology	Siewert 2	485		27
[78]	Tsuji	2004	cross-sectional	Osaka, Japan	NR	surgical resection pathology	pathology	Siewert 2	23		2
[62]	Van Sandick	2000	cross-sectional	Amsterdam, Netherlands	1/1993–1/1998	surgical resection pathology (only pT1 cancers)	pathology		12		12
[64]	Wijnhoven	1999	cross-sectional	Rotterdam, Netherlands	1987–1997	surgical resection pathology	pathology	Siewert 2	141		18
Multi-center Studies											
[72]	Borg	2016	case series	Lund & Malmo, Sweden	1/2006–12/2010	surgical resection pathology	pathology	NR	45		11
[80]	Huang	2011	cross-sectional	Nanjing, China and Boston, Massachusetts	2004–2008, 1991–2008, 1999–2008	surgical resection pathology	pathology	within 2 cm of OGJ	70		26
[81]	Imamura	2019	case series	Tokyo, Kumamoto, Fukuoka, Japan	2006–2013	surgical resection pathology	pathology	Siewert 2	273		69
[79]	Yuasa	2006	case series	Nagoya, Japan	1987–2003	surgical resection pathology	pathology	Siewert 2	40		2
Population-based Studies											
[56]	Rantanen	2016	cross-sectional	Finland	1980–2007	biopsy/surgical resection pathology	EGD/pathology	NR	154	4	24

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