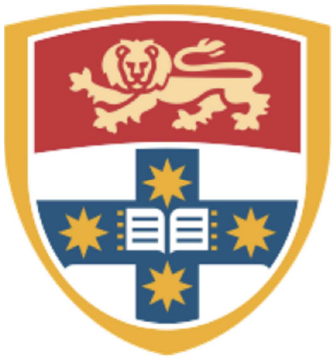
THE UNIVERSITY OF SYDNEY

BARRETT'S ESOPHAGUS AND ITS ASSOCIATION WITH HIATAL HERNIA, CIGARETTE SMOKING AND COLONIC TUMORS

A thesis submitted in fulfillment of

the requirements for the degree of

Master of Philosophy (Medicine)



Department of Medicine

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"...progress is not static and there is no subject which does not yield more knowledge as the depths are sounded."

N. R. Barrett, 1957

Statement of Originality

The contents of this thesis represents original research undertaken by the author from the Whiteley-Martin Research Centre, Sydney Medical Program, University of Sydney, Australia.

The author was responsible for the design, development and conduct of the work which was performed under the joint supervision of Associate Professor Guy Eslick and Professor Michael Cox.

All literature searches, data extraction and interpretation were completed by the author unless otherwise acknowledged. Literature searches and data extraction were also independently performed by Dr Martin Tio. Data analysis was completed by the author in association with Associate Professor Guy Eslick.

Declaration: To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Certification

I hereby certify that the work embodied in this thesis is the result of original research and has not been submitted for a higher degree to any other University or Institution.

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Juliana Andrici

LIST OF PUBLICATIONS INCLUDED AS PART OF THE THESIS

- Andrici J, Tio M, Cox MR, Eslick GD. Hiatal hernia and the risk of Barrett's esophagus. *Journal of Gastroenterology and Hepatology*. 2013; 28(3):415-431.

- Andrici J, Cox MR, Eslick GD. Cigarette Smoking and the Risk of Barrett's Esophagus: A Meta- Analysis. *Journal of Gastroenterology and Hepatology* 2013; 28(8):1258-73.

- Andrici J, Tio M, Cox MR, Eslick GD. Meta-analysis: Barrett's oesophagus and the risk of colonic tumours. *Alimentary Pharmacology & Therapeutics.* 2013; 37: 401-410.

LIST OF ADDITIONAL PUBLICATIONS RELEVANT TO THE THESIS BUT NOT FORMING PART OF IT

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- Andrici J, Eslick GD, Cox MR. Barrett's Esophagus and the risk of colonic tumors: a systematic review and meta-analysis. *Journal of Gastroenterology and Hepatology*. 2011; 26 (Suppl. 4): 82.

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- November 2012 6th Australian Health and Medical Research (AHMR) Congress, Adelaide Convention Centre, Adelaide, Australia. Poster presentation. Andrici J, Tio M, Eslick GD, Cox M. *Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis.*

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- September 2012 11th OESO World Congress on Diseases of the Esophagus, Grand Hotel Como & Congress Centre, Como, Italy. Poster Presentation. Andrici J, Eslick G, Cox M. *Cigarette Smoking and the Risk of Barrett's Esophagus: A Meta-Analysis.*

- September 2012 11th OESO World Congress on Diseases of the Esophagus, Grand Hotel Como & Congress Centre, Como, Italy. Poster Presentation. Andrici J, Tio M, Eslick G, Cox M. *Barrett's Esophagus and the Risk of Colonic Tumors: A Meta-Analysis.*

- September 2011 Australian Gastroenterology Week, Brisbane Convention & Exhibition Centre, Brisbane, Queensland, Australia. Poster Presentation. Andrici J, Eslick G, Cox M. *Hiatal Hernia and the Risk of Barrett's Esophagus: A Systematic Review and Meta-Analysis.*

- September 2011 Australian Gastroenterology Week, Brisbane Convention & Exhibition Centre, Brisbane, Queensland, Australia. Oral Presentation. Andrici J, Eslick G, Cox M. *Barrett's Esophagus and the Risk of Colonic Tumors: A Systematic Review and Meta-Analysis.*

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Introduction and Aims

Barrett's esophagus (BE) is a premalignant condition to esophageal adenocarcinoma involving metaplasia of the esophageal epithelium. Since BE was first identified and described, it has been closely associated with hiatal hernia. The strength of the relationship has never been quantified, nor has the association, adjusted for confounders such as obesity and reflux, been examined. Male gender, obesity and reflux are well recognized risk factors for BE, however it is less certain what role environmental factors such as cigarette smoking play in the development of the condition. The association of BE with colonic tumors has also been speculated on but not clearly established. The aim of this thesis was to further explore the epidemiology of BE, specifically the relationship between BE and hiatal hernia, cigarette smoking and colonic tumors, through meta-analyses.

Methods

Three meta-analyses and systematic reviews were conducted, quantifying the relationship between BE and hiatal hernia, cigarette smoking and colonic tumors, respectively. Four electronic databases (Medline, PubMed, Embase, and Current Contents Connect) were searched for observational studies of BE patients. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random effects model for the association BE with hiatal hernia, cigarette smoking and colonic tumors.

Results

A positive relationship was observed between BE and hiatal hernia, which remained even after adjusting for reflux. Cigarette smoking was associated with an increased risk of BE. This was reflected in subgroup analyses of ever-, current- and former-smokers. BE was also associated with colonic tumors. The relationship was observed with both benign adenomatous tumors as well as with colorectal cancer, though it was stronger for colorectal cancer.

Conclusions

The association between BE and hiatal hernia is stronger for long segment BE when compared with short segment BE, and it appears to be independent of reflux. BE patients are also more likely to have ever smoked cigarettes. BE is associated with colonic tumors, with the association being stronger with colorectal cancer than with benign lesions.

CHAPTER 1

BACKGROUND AND INTRODUCTION

Symptoms suggestive of esophagitis and gastroesophageal reflux had been described in the medical literature since at least as early as the late 1800's,[1] and the existence of "peptic ulcers" of the esophagus were known about by the beginning of the twentieth century.[2] The presence of "ectopic gastric epithelium" in the esophagus had also been documented by Schridde[3] in 1904 and Taylor[4] in 1927. These were described as discrete round to oval lesions up to three-quarters of a inch in diameter, reminiscent of shallow erosions or ulcers; they were pink or red in color with centers which were slightly depressed below the level of the esophageal epithelium, with raised margins, and were typically found on the posterior aspect of the upper esophagus.[3,4] However the recognition of what was later to become known as Barrett's esophagus (BE) as a distinct disease entity began in 1950 with a description of esophageal ulceration arising from a zone of gastric-type mucosa by the thoracic surgeon Norman Barrett.[5] Allison and Johnstone[6] used the term "lower esophagus lined with gastric mucous membrane" to describe the presence of gastric mucosa, including gastric glands, in the lower esophagus and confirmed the location of the lesion as being the esophagus itself, rather than stomach herniating into the thoracic cavity. Barrett subsequently used the term "lower esophagus lined by columnar epithelium" in his 1957 paper which more thoroughly described the disease.[7] He differentiated this lesion from Taylor's discrete "ectopic islets" in that the columnar cells lining the esophagus continued upward in an "unbroken sheet" from the esophagogastric junction, and extended from only a few centimeters above the junction in some cases, to the upper esophagus in others.

Currently, North American guidelines stipulate that a diagnosis of BE is made when columnar mucosa is identified above the gastroesophageal junction on endoscopy and is confirmed to contain specialized intestinal epithelia (characterized by the presence of

goblet cells) on histological examination.[8] Since 1994, BE has been classified as either short segment BE (SSBE) or long segment BE (LSBE), depending on the extent of metaplastic change observed on endoscopic examination, as measured from the gastroesophageal junction.[9]

In their 1953 paper, Allison and Johnstone[6] described a patient with adenocarcinoma which developed within the section of the esophagus lined by gastric mucosa. Both Allison and Johnstone[6] as well as Taylor[4] speculated on the "penetration" of gastric ectopic tissue within the esophagus and the potential for subsequent malignant transformation, and although early case reports[10] were published linking the columnar-lined esophagus with adenocarcinoma, it was only in the 1970's that the link was more definitively established.[11-13] BE has since emerged as a clinically significant entity due to its role as the premalignant lesion of esophageal adenocarcinoma,[14,15] a disease which although uncommon in absolute terms, has not only experienced a dramatic increase in incidence in recent decades,[16-21] but also carries an extremely poor prognosis.[22,23] As a result, patients with known BE are monitored by undergoing regular upper endoscopies with biopsy to check for dysplasia. Further study into risk factors and epidemiological associations of BE, which are at present not well understood, is warranted. It is against this background that the work contained in this thesis was embarked upon. I sought to examine the relationships between BE and various factors, some of which have been either closely associated with BE, such as hiatal hernia, and others speculated on, such as an association with colonic tumors and cigarette smoking.

Hiatal hernia involves prolapse of elements of the abdominal cavity, most commonly parts of the stomach, through the esophageal hiatus of the diaphragm and into the thoracic cavity. It results in anatomical impairment of the esophagogastric junction, leading to reflux of gastric material into the esophagus, including hydrochloric acid and pepsin as well as pancreatic enzymes and bile, which are thought damage the esophageal epithelium and contribute to the metaplasia resulting in BE.[24,25] This mechanism has been speculated on since BE was first recognized. Barrett wondered at the location of the lesion and why it should always be found in the lower esophagus; he postulated that continued exposure to gastric juices as a result of an incompetent gastroesophageal sphincter could erode the normal esophageal squamous epithelium, which was then replaced by columnar epithelium.[7] Allison and Johnstone[6] reported the prevalence of hiatal hernia in all of the elderly patients with "lower esophagus lined with gastric mucous membrane" which constituted their 1953 case series. In agreement, Barrett also made the connection between the columnar lined esophagus and sliding hiatal hernia and reflux; in fact he felt that the association was strong enough to warrant an explicit clarification in his 1957 paper that sliding hiatal hernia and columnar lined esophagus were separate entities.[7] Since then, the association between hiatal hernia and columnar or specialized intestinal metaplasia of the esophagus has become well established in the literature.[26-28] The purpose of conducting a meta-analysis on the association between hiatal hernia and BE was twofold. Firstly, as no meta-analysis on the subject has been performed to date, we wanted to quantify the relationship. Secondly, we wanted to observe through subgroup analyses whether an association between hiatal hernia and BE remained after adjusting for important confounding variables. Two important risk factors for BE, namely obesity and gastroesophageal reflux disease (GERD)[26-30] are also associated with hiatal hernia. The mechanism of obesity, especially central adiposity, increasing abdominal pressure

and contributing to both hiatal hernia and reflux, and of hiatal hernia enabling reflux which in turn is thought to contribute to the development of BE, is very plausible. We thus aimed to conduct subgroup analyses looking at studies which adjusted for obesity and reflux, to see if the association between hiatal hernia and BE remained, independently of these confounders.

While male gender, obesity and reflux are well recognized risk factors for BE,[29] it is less certain what role environmental factors play in the development of BE. Smoking is a known risk factors for squamous cell esophageal carcinoma,[31] however its association with adenocarcinoma, although suspected,[31-34] is less well established. Furthermore, cigarette smoking has not been definitely linked with an increased risk of developing BE. The literature results are currently mixed, with some studies showing a positive association,[30,35-37] while others report no association.[38-42] A recent analysis of 5 case control studies from the International Barrett's and Esophageal Adenocarcinoma Consortium ("BEACON")[43] found a positive relationship between cigarette smoking and BE, thus providing a strong indicator that an association is present. To date no meta-analysis of the relationship between cigarette smoking and BE has been performed. We conducted a meta-analysis examining the relationship between smoking and BE, specifically using subgroup analyses to determine whether a dose response exists, and whether the relationship changes depending on smoking status (current versus former versus ever smokers).

The possibility of an association between BE and an increased risk of colonic tumors was first raised by Sontag et al in 1985.[44] This is a clinically significant question because if a

relationship is found, it carries implications in terms of screening BE patients for colorectal cancer (CRC). Since then, several studies have reported conflicting results. Although a systematic review in 1995[45] showed a strong association, the association is not well established and there is disagreement in the literature as to the impact of its findings. Since then, several new studies have been published reporting the prevalence of colonic tumors in patients with BE and therefore we considered it appropriate to perform a meta-analysis that also incorporated these studies. We hoped to provide greater insight into this possible association as well perform subgroup analyses to explore whether adjustment for confounding factors such as obesity (a risk factor common to both BE and CRC) had any impact on the association.

In summary, the overarching theme of this thesis is the epidemiology of BE. Three meta-analyses have been conducted examining and quantifying, respectively, the association between BE and hiatal hernia, cigarette smoking, and colonic tumors. It is hoped that this work will contribute towards the body of knowledge on BE and its risk factors and associations.

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CHAPTER 2

HIATAL HERNIA AND THE RISK OF BARRETT'S ESOPHAGUS

INTRODUCTION

Barrett's Esophagus (BE) is a condition in which the normal squamous esophageal lining is replaced by specialized or intestinal columnar epithelium.[1,2] According to current guidelines in North America,[3] BE is diagnosed when columnar mucosa is identified above the gastroesophageal junction on endoscopy and is confirmed to contain specialized intestinal epithelia (characterized by the presence of goblet cells) on histological examination. Since 1994, BE has been classified as either short segment BE (SSBE) or long segment BE (LSBE) according to the length of the metaplastic change observed on endoscopic examination.[4] If the intestinal metaplasia extends less than 3 cm above the gastroesophageal junction, it is termed SSBE, and if it extends 3 cm or more, it is termed LSBE. The prevalence of BE in the general US population is uncertain, due to the fact that many individuals are asymptomatic, and because diagnosis requires endoscopy. A study from Sweden found a prevalence of 1.6% in a random sample of 3000 individuals from the general population.[5] Among patients with gastroesophageal reflux disease (GERD), the prevalence of BE has been reported to be between 3% and 15%.[6,7] The clinical significance of BE is its association with an increased risk in developing esophageal adenocarcinoma.[8,9] Although esophageal adenocarcinoma is a relatively uncommon disease, its incidence has been increasing in the US and other Western countries in recentdecades.[10–15]

Risk factors for BE include white race, male sex, older age, obesity[16] and persistent gastroesophageal reflux.[17] Hiatal hernia has also been associated with BE. Hiatal hernia refers to the prolapse of elements of the abdominal cavity, most commonly parts of the stomach, through the esophageal hiatus of the diaphragm and into the thoracic cavity. The most common type is Type I, or sliding hernia, in which the lower esophageal

sphincter and a portion of the gastric cardia herniate upwards due to a widening of the muscular hiatal aperture and circumferential laxity of the phrenoesophageal membrane.[18–20] The presence of hiatal hernia results in anatomical impairment of the esophagogastric junction, which leads to reflux of gastric material into the esophagus. This includes gastric products such as hydrochloric acid and pepsin, as well as pancreatic enzymes and bile.[17,19] It is hypothesized that chronic exposure to these substances is a contributing factor to the development of BE.

Although individual studies have shown a higher prevalence of hiatal hernia in BE patients compared with non-BE GERD patients,[21–23] to date no meta-analysis of the relationship between BE and hiatal hernia has been performed. The purpose of this study was to conduct a meta-analysis combining the results of studies reporting the prevalence of hiatal hernia in BE subjects, and thus provide a quantitative estimate of the increased risk of BE associated with hiatal hernia. We hypothesized that hiatal hernia is associated with an increased risk BE, and that we would see a stronger association with LSBE than with SSBE.

METHODS

Literature search strategy

We followed the PRISMA Statement for Systematic Reviews and Meta-Analyses in performing our systematic review.[24] A systematic search was performed by two reviewers (J.A. and M.T.) through four electronic databases (Medline [1950 – present], PubMed [1950 – present], Embase [1947 – present], and Current Contents Connect [1998 – present]) to 4 April 2012, for observational studies of Barrett's esophagus

patients, to identify relevant articles. The search used the terms “Barrett’s Esophagus” or “Barrett’s Esophagus” and “hiatal hernia” or “hiatus hernia”, which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed and authors were not contacted for missing data.

Inclusion and exclusion criteria

We included studies that met the following inclusion criteria: (i) BE was recognized on endoscopy and confirmed histologically as specialized intestinal metaplasia (SIM). Where studies reported on multiple subgroups, such as endoscopically suspected non-SIM BE cases and SIM BE cases, only the SIM BE cases were included in our analyses; (ii) the risk point estimate was reported as an odds ratio (OR), or the data were presented such that an OR could be calculated; (iii) the 95% confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; (iv) an internal control group was used when calculating the risk estimate; (v) the total sample size of the study exceeded 50 patients. We excluded studies that did not meet the inclusion criteria. Studies were included or excluded following consensus between three authors (J.A., M.T. and G.E.).

Data extraction

We performed the data extraction via as standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction of the study (prospective or retrospective), control

groups used, population type, country, continent, economic development, case control matching, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, and CIs or data used to calculate CIs, the type of BE investigated (SSBE or LSBE), and size of hernia. We selected only subjects with SIM to serve as the BE cases in our analysis. Where BE length was not stated, the study was included in the any length BE analysis. Adjusted ratios were extracted in preference to non-adjusted ratios; however, where ratios were not provided, unadjusted ORs and CIs were calculated. Where more than one adjusted ratio was reported, we chose the ratio with the highest number of adjusted variables. Where multiple risk estimates were available in the same study, for example, when studies reported on the risk estimates of different lengths of BE, or when risk estimates were reported for different control groups, they were included as separate risk estimates. Statistical analysis. Pooled OR and 95% CIs were calculated for the effect of hiatal hernia on the risk BE using a random effects model.[25] This was performed for the association between hiatal hernia and any length BE. Where a study reported risk estimates for different control groups (for example, a GERD control group, a non-GERD control group, and a combined control group comprising both GERD non-GERD controls), we included the risk estimate for the combined control group where possible, with the separate control groups included in a subgroup analysis.

Subgroup analyses by length of BE, adjustment of ORs, study type, and continent were also performed. In particular, we performed subgroup analyses by studies that adjusted for body mass index (BMI) and reflux, both independent risk factors for BE. Where a single study reported multiple ORs for different sized hernias (that is, different risk estimates associated with different sized hernias), we computed a pooled OR from the

multiple ORs and used that figure as the OR for that study. We quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies, which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively.[26] We performed sensitivity analyses, with individual studies excluded one at a time, when statistically significantly heterogeneity was detected. Publication bias was quantified using the Egger's regression model,[27] and if statistically significant publication bias was detected, the effect of bias was assessed using the fail-safe number method and the trim-and-fill method. The failsafe number represents the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P < 0.05$ level. Publication bias is generally regarded as a concern if the fail-safe number is less than $5n + 10$, with n being the number of studies included in the meta-analysis.[28]The trim-and-fill method adjusts for potential unpublished studies in the meta-analysis by augmenting the observed data to create a more symmetric funnel plot. New pooled ORs are then calculated and compared to the original pooled OR, and similarity between the two decreases the likelihood that publication bias significantly affected the meta-analysis results. Results were regarded as statistically significant if $P < 0.05$. All analyses were performed with Comprehensive Meta-analysis (version 2.0).

RESULTS

Study characteristics

From 1428 studies initially identified,33[21–23,29–58] met our inclusion criteria (Fig. 1). Selected characteristics of the included studies are presented in Table 1. The studies represented a variety of geographical regions, with seven studies looking at European

populations, 13 studies examining Asian populations, 11 studies examining North American populations and two studies examining South American populations. In terms of study design, 26 studies were cross-sectional studies, and seven were case control studies. Sample sizes ranged from 102 to 18 766, and BE cases ranged from 9 to 1215. Overall, there were 4390 BE patients and 51 748 participants.

Any length Barrett's Esophagus

Thirty-one studies comprising 3327 BE cases with a total of 47 461 individuals were included in the meta-analysis for any length BE. We found an increased risk of any length BE in patients with hiatal hernia, with pooled OR of 3.94 (95% CI, 3.02–5.13) (Fig. 2). There was statistically significant heterogeneity (I^2 = 82.03%, P < 0.001). A sensitivity analysis did not find any one study which contributed significantly to the heterogeneity. The Egger test for publication bias was significant (P = 0.0005), and this is depicted visually on a funnel plot (Fig. 3). However the fail-safe number was 3502 studies, and the trim-and-fill method showed an imputed risk estimate of OR 2.88; 95% CI, 2.23–3.72, which was lower than the observed risk estimate but still statistically significant. We therefore concluded that publication bias existed, but was minimal. We performed subgroup analyses by different study characteristics, namely the control groups used, the adjustment of ORs, the continent where the study was conducted and the study type (Table 2). The subgroup analysis by control group showed a risk estimate for BE patients when compared to GERD controls of OR 3.65; 95% CI, 2.74–4.85, and OR 13.73; 95% CI, 3.54–53.22 when compared with non-GERD controls. The pooled ORs for the various continents were as follows: Europe (OR 7.93; 95% CI, 3.39–18.58); North America (OR 3.38; 95% CI, 1.95–5.86); Asia (OR 3.84; 95% CI, 2.48–5.94); South America (OR 12.14; 95% CI, 3.27–45.13). A subgroup analysis looking only at the

13studies[23,29,30,34–36,38,39,42,43,56,57] which reported adjusted ORs showed an increased risk of any length BE associated with hiatal hernia (OR 2.99; 95% CI, 2.24–3.98). A further subgroup analysis looking specifically at the four studies[30,38,39,57] which adjusted for BMI, a risk factor common to both hiatal hernia and BE, also showed an association between hiatal hernia and any length BE (OR 2.63; 95% CI, 1.85–3.76). There was no significant heterogeneity (I^2 = 11.16%, P = 0.337), and no publication bias(P = 0.227). When stratified by adjustment for reflux, a pooled analysis of the seven studies[23,29,30,34,39,42,47] which adjusted their ORs for reflux, a major risk factor for the development of BE, the risk estimate remained increased (OR 3.35; 95% CI, 2.25– 4.39). There was no heterogeneity (I^2 = 0%, P = 0.995), and no publication bias (P = 0.444). The subgroup analysis of the 19 studies[21,31–33,35,40,41,44–46,48–55,58] which did not provide adjusted ORs also showed an increased risk (OR 4.26; 95% CI, 2.82–6.43). When stratifying by study type, the increased risk remained, though it was greater for case control studies (OR 4.38; 95% CI, 2.91–6.61) than for cross-sectional studies (OR 3.66; 95% CI, 2.72–4.91).

Short segment Barrett's Esophagus

Nine studies comprising of 1019 BE cases with a total of 6357 individuals reported an association between hiatal hernia and SSBE and were included in the SSBE meta-analysis. We found an increased risk of SSBE in patients with hiatal hernia, with pooled OR of 2.87 (95% CI, 1.75–4.70) (Fig. 4). There was statistically significant heterogeneity (I^2 = 81.15%, P < 0.001), which became insignificant when Conio et al[36] was removed on sensitivity analysis (I^2 = 47.90%, P = 0.062), while the risk estimate was not changed significantly (OR 2.29; 95% CI, 1.64–3.20). The Egger test for publication bias was not significant (P = 0.888), and the fail-safe number was 259 studies. Subgroup analyses by control group, adjusting variables continent and study type were performed (Table 2).

The subgroup analyses comparing SSBE subjects to GERD controls and non-GERD controls both showed an increased risk, (OR 1.86; 95% CI, 1.16–2.97) and (OR 7.93; 95% CI, 2.05– 30.59) respectively. When stratified by continent, the pooled risk estimates for Europe and North America (the only two continents with more than one study reporting an association between SSBE and hiatal hernia), were (OR 3.40; 95% CI, 0.53–21.89) and (OR2.82; 95% CI, 2.35–3.37) respectively. Subgroup analyses for adjusted ORs could not be performed for SSBE because of a lack of data, but the pooled risk estimate for the studies which did not provide adjusted ORs was OR 2.85; 95% CI, 1.43–5.67. The subgroup analysis by study type was as follows: case control studies (OR 5.35; 95% CI, 1.74–16.47) and cross-sectional studies (OR 1.96; 95% CI, 1.29–2.99).Long segment Barrett's Esophagus. Nine studies comprising of 648 BO cases with a total of 8233 individuals reported an association between hiatal hernia and LSBE and were included in the LSBE meta analysis. We found an increased risk of LSBE in patients with hiatal hernia, with pooled OR of 12.67 (95% CI, 8.33–19.25) (Fig. 5). There was no significant heterogeneity (I^2 = 31.95%, P = 0.162). The Egger test for publication bias was not significant (P = 0.929), and the fail-safe number was 520 studies. Subgroup analyses by control group, adjusting variables continent and study type were performed (Table 2). The subgroup analyses comparing LSBE patients with GERD controls and non- GERD controls both showed an increased risk, (OR 11.17; 95% CI, 6.38–19.55) and (OR 13.44; 95% CI, 8.26–21.87) respectively. When stratified by continent, only studies from North America reported on the association between hiatal hernia and LSBE, and the pooled risk estimate was OR 13.22; 95% CI, 9.63–18.14. Looking at studies that reported adjusted ORs, a subgroup analysis of the three studies[29,31,34] which reported adjusted ORs showed an increased risk of LSBO associated with hiatal hernia (OR 13.70; 95% CI, 9.61–19.54). Two studies[29,34] adjusted for reflux, and the pooled risk estimate of those studies showed an OR of 13.84;95% CI, 5.19–36.89. The subgroup analysis of the six

studies[21,33,36,44,45,49] which did not provide adjusted ORs also showed an increased risk (OR 11.97; 95% CI, 5.53–25.88). When stratified by study type, the risk estimates were OR 13.35; 95% CI, 9.62–18.53 for the case control subgroup and OR 11.30; 95% CI, 5.06–25.21 for the cross-sectional subgroup.

DISCUSSION

Our systematic review and meta-analysis show what appears to be a strong relationship between hiatal hernia and BE, with the strength of the association being most profound in the LSBE group. It is plausible that hiatal hernia increases the risk of BE through increased esophageal exposure to gastric contents such as acid and bile,[19,59,60] and therefore BE is more likely to be present in individuals with hiatal hernia. The idea that initial damage to esophageal epithelium followed by exposure to either acid alone or acid and bile results in metaplasia is supported by animalmodels.[61–63] In addition, Champion et al[64] and Vaezi et al[59,60] found that in humans, acid and duodenogastroesophageal reflux occur together with possible synergistic effects and that such reflux is increased in patients with BE. It is therefore likely that the presence of hiatal hernia contributes to the development of BE through the mechanism of increased esophageal exposure to gastric contents. We also observed a stronger relationship between hiatal hernia and LSBE, compared with SSBE or any length BE. For the longer segment of BE to develop, the environment of increased reflux provided by the chronic presence of hiatal hernia may be a significant contributing factor, in which case hiatal hernia would be expected to be present in the majority of patients with LSBE. This has been found to be the case by severalinvestigators.[21–23] The association of prolonged esophageal acid exposure and decreased esophageal sphincter pressure,

both of which result from hiatal hernia,[18,65] with BE length, have indeed been reported.[66–68]

Even though we have observed strong positive relationships in our meta-analyses, we have identified a number of issues pertaining to our study that impact on the interpretation of our results. First, the results may be subject to confounders as several risk factors, notably age, gender and obesity, are common to both hiatal hernia and BE. While we have used adjusted ORs when available, some studies did not report adjusted ORs, and therefore our analyses include both adjusted and unadjusted ORs. To assess whether this has had a significant impact on our final results, we performed several subgroup analyses looking at studies that reported adjusted ORs. There was no appreciable difference in risk estimates between the subgroup analysis of studies that reported adjusted ORs compared with the overall result for either any length BE or LSBE. Obesity in particular is recognized as a risk factor common to both hiatal hernia and BE;[16,69] however, the subgroup analysis of studies that adjusted for BMI, a measure of obesity, resulted in a risk estimate for any length BE, which was similar to the overall pooled OR. The subgroup analyses comparing BE subjects to GERD and non-GERD controls showed a marked increase in risk for the comparison with non-GERD controls. This implies that hiatal hernia is more common among GERD patients than non-GERD patients, and suggests a common etiology between hernia and the conditions of GERD and BE, which is something that is already acknowledged in the literature.[20] Since GERD is also a significant risk factor in the development of any length BE, we conducted a subgroup analysis including only the studies that reported ORs adjusted for reflux, which showed a positive relationship (OR 3.35; 95% CI, 2.25–4.39), with the association being very close to that observed in the overall risk estimate for any length BE when

including all the studies (OR 3.94). This was also observed when stratifying for studies reporting on LSBE, which adjusted for reflux, with the subgroup risk estimate not differing appreciably from the overall risk ratio for LSBE (OR 13.84 vs OR 12.67). These results show that even after adjusting for clinically important confounding factors, the relationship between BE and hiatal hernia remains significant, and this adds strength to the hypothesis that the relationship is a real one.

Second, since both hiatal hernia and BE are recognized at endoscopy, there is the possibility of referral bias skewing the results towards a more positive association. This is because upper endoscopy is a diagnostic tool for both conditions, so they are more likely to be discovered incidentally in a population that is referred for this procedure.

Additionally, upper endoscopy is an invasive procedure that carries risks and therefore ethical issues exist around performing it on members of the general population in the absence of any indications. The populations studied therefore necessarily consist of symptomatic patients in whom it is more likely that pathology will be found, so this is another potential source of bias affecting our results.

In addition, our analysis is based on cross-sectional and case control studies, which are retrospective in nature, and therefore subject to the biases inherent in retrospective studies. If the association between hiatal hernia and BE is a real one, the temporal relationship is likely to be one of presence of hiatal hernia leading to the development of BE. In that case, the ideal study type would be one that recruited patients with hiatal hernia but without BE, as well as a control group who did not have hiatal hernia, and

prospectively observed both groups for development of BE. There are, however, several difficulties in performing such a study. One problem is finding appropriate cases, as patients are usually not investigated for hiatal hernia specifically, but this is rather an incidental finding. Second, there is the issue of performing regular endoscopies on patients with hiatal hernia to observe for the development of BE, as screening endoscopy is not currently an indication in the management of hiatal hernia. Third, the choice of control group would be problematic. Once again, endoscopy is not indicated as a screening tool in asymptomatic individuals without a prior diagnosis of esophageal pathology, thus creating ethical issues around performing endoscopies to monitor for the development of BE in patients in whom such an intervention is not otherwise indicated.

The size of our study was another limitation. While we identified 33 studies overall, the subgroup analysis were based on a smaller number of studies (nine for each of SSBE and LSBE). The numbers of LSBE patients were also considerably smaller, with only 648 subjects identified, compared with 1019 SSBE patients and 3327 patients with any length BE. In addition, while the number of studies was not low, the number of BE cases in most of the studies was small. With the exception of one study,[34] none of the studies reported on the size of the hiatal hernia. The size of the hernia could affect the strength of the relationship, and we would have liked to perform subgroup analyses on different sized hernia groups if the data were available.

We observed a high degree of heterogeneity in the any length BE meta-analysis (I^2 = 82.03%, $P < 0.001$), which was not found on sensitivity analysis to be contributed to by any one study, but which we believe can be explained by the grouping together of

patients with varying lengths of BE. Our subgroup analysis found pooled ORs of 2.87 and 12.67 for SSBE and LSBE respectively, so we expected that an analysis of studies that looked simply at the presence of BE of any length would show considerable heterogeneity. Historically, in the early 1980s a 3cm rule introduced to prevent over diagnosis of BE stipulated that a minimum of3 cm of metaplasia above the observed gastroesophageal junction be required for the diagnosis of BE.[17] This would have resulted in only patients with what we now classify as LSBE being diagnosed, with SSBE patients not being diagnosed. We had one study from the 1980s,[51] which reported data for BE of unspecified length and was included in the any length BE analysis. Given the time period during which this study was conducted, the cases are likely to be what we now classify as LSBE. However, a sensitivity analysis excluding this study did not significantly alter the heterogeneity. The heterogeneity in the SSBE analysis (I^2 = 81.15%, P < 0.001) became insignificant when Conio et al[36] was excluded on sensitivity analysis (I^2 = 47.90%, P = 0.062), with the risk estimate experiencing minimal change (OR 2.29; 95% CI, 1.64–3.20). We were unsure as to why this study contributed to the heterogeneity, but it was an outlier in terms of its risk estimate when compared with the ORs of the other studies included in that analysis (this can be seen graphically in Fig. 4). We speculated that some heterogeneity in this group may be due to the increased uncertainty in the diagnosis of SSBE as opposed to LSBE. The difficulty in precisely localizing and measuring the squamocolumnar junction during endoscopy, which is more crucial to the diagnosis of SSBE than LSBE, is well recognised.[70,71] This may result in patients being wrongly diagnosed as having or not having SSBE.

We performed an additional analysis grouping the studies by geographical location and study types (Table 2). There were consistent risk estimates between continents in the

any length BE analysis, with the exception of South America, which consisted of two studies and found a much higher association than in the remaining continents. The subgroup analysis by study type showed consistently higher risk estimates in the case control subgroups for all lengths of BE compared with the cross-sectional subgroups. This raises the possibility that the case control studies are overestimating the risk and therefore inflating our results. However, given that our meta-analysis contained mostly cross sectional studies and our overall pooled ORs did not differ substantially from the cross-sectional subgroup risk estimates in all lengths of BE, we did not consider this to be a significant source of bias.

The Egger test for publication bias was significant in the any length BE. However, the fail-safe numbers were 3502, and given our thorough search methodology, we thought it unlikely that so many studies would have been missed. In addition, the trim-and-fill method showed that the observed values were similar to the imputed values (OR 2.88 vs OR 3.94).We therefore concluded that publication bias existed in our analysis, but that it was minimal.

Our study had a number of strengths. The PRISMA guidelines were followed. We performed a thorough search through four databases with no language restrictions. Small studies with less than 50 total participants were excluded. We also excluded studies using external control groups. The use of an internal control group is recognized as a more statistically robust way of study design,[72–74] and the exclusion of studies using external comparators adds rigor to our analysis.

In summary, our results show that hiatal hernia is associated with an increased risk of BE, even after adjusting for significant confounders such as reflux and BMI. Hiatal hernia was associated with any length of BE; however the association was significantly greater with LSBE.

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Table 1: Barrett's esophagus studies included in the Systematic Review

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Abrams et al[29] (2008) 1a	2008	Cross-sectional	USA	Patients undergoing upper endoscopy with histologically confirmed BE	Patients undergoing upper endoscopy without BE	Age, gender, race, indication for endoscopy	9	2100	LSBE
Abrams et al[29] (2008) 1b	2008	Cross-sectional	USA	Patients undergoing upper endoscopy with histologically confirmed BE	Patients undergoing upper endoscopy without BE	Age, gender, race, indication for endoscopy	92	2100	Any Length BE
Amano et al[30](2006)	2006	Cross-sectional	Japan	Consecutive patients undergoing EGD with histologically confirmed BE	Consecutive patients undergoing EGD for their annual medical check-up or for the investigation of their GI symptoms	Age, gender, BMI, green tea consumption, fatty food consumption	106	1668	Any length BE
Avidan et al[22] (2002)	2002	Case Control	USA	Symptomatic GERD patients with histologically confirmed BE	Patients with symptomatic GERD, but with histologically proven absence of BE and endoscopic absence of erosive esophagitis, esophageal ulcer, or peptic stricture	None	256	485	Any Length BE
Avidan et al[31](2001) 1a	2001	Case Control	USA	Patients undergoing upper endoscopy with histologically confirmed BE	Patients without symptoms of GERD and with normal esophageal mucosa during EGD	Age, gender, Caucasian ethnicity, smoking, alcohol consumption, prior gastric surgery	650	4063	SSBE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Avidan et al[31](2001) 1b	2001	Case Control	USA	Patients undergoing upper endoscopy with histologically confirmed BE	Patients without symptoms of GERD and with normal esophageal mucosa during EGD	Age, gender, Caucasian ethnicity, smoking, alcohol consumption, prior gastric surgery	366	4063	LSBE
Banki et al[32] (2005)	2005	Cross-sectional	USA	BE patients	Patients with abnormal 24-hour pH tests without BE	None	186	506	Any Length BE
Byrne et al[33] (1999) 1a	1999	Cross-sectional	UK	Symptomatic patients with histologically confirmed BE attending clinic for open-access endoscopy	Symptomatic patients without BE attending clinic for open-access endoscopy	None	15	225	SSBE
Byrne et al[33] (1999) 1c	1999	Cross-sectional	UK	Symptomatic patients with histologically confirmed BE attending clinic for open-access endoscopy	Symptomatic patients without BE attending clinic for open-access endoscopy	None	8	225	LSBE
Byrne et al[33] (1999) 1b	1999	Cross-sectional	UK	Symptomatic patients with histologically confirmed BE attending clinic for open-access endoscopy	Symptomatic patients without BE attending clinic for open-access endoscopy	None	23	225	Any Length BE
Cameron et al[21] (1999) 1a	1999	Case Control	USA	Patients referred for upper GI endoscopy for clinical indications, patients with histologically confirmed BE	Consecutive patients referred for endoscopy either with symptoms of reflux or for non-reflux symptoms, without histologically confirmed BE	None	18	167	SSBE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Cameron et al[21] (1999) 1b	1999	Case Control	USA	Patients referred for upper GI endoscopy for clinical indications, patients with histologically confirmed BE	Consecutive patients referred for endoscopy either with symptoms of reflux or for non-reflux symptoms, without histologically confirmed BE	None	46	167	LSBE
Cameron et al[21] (1999) 1c	1999	Case Control	USA	Patients referred for upper GI endoscopy for clinical indications, patients with histologically confirmed BE	Consecutive patients referred for endoscopy either with symptoms of reflux or for non-reflux symptoms, without histologically confirmed BE	None	64	167	Any Length BE
Campos et al[34] (2001) 1a	2001	Cross-sectional	USA	Patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring, with histological evidence of BE	Patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring, without histological evidence of BE	None	67	502	SSBE
Campos et al[34] (2001) 1b	2001	Cross-sectional	USA	Patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring, with histological evidence of BE	Patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring, without histological evidence of BE	Defective LES, gender, number of reflux episodes	107	502	LSBE
Campos et al[34] (2001) 1c	2001	Cross-sectional	USA	Patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring, with histological evidence of BE	Patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring, without histological evidence of BE	Abnormal bilirubin exposure, defective LES, gender, defective distal contraction amplitude, number of reflux episodes longer than 5 minutes, duration of GERD symptoms	174	502	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Chacaltana et al[35] (2009) 1a	2009	Case Control	Peru	Patients participating in a gastric cancer screening campaign, with histologically confirmed BE	Patients participating in a gastric cancer screening campaign, without symptoms of GERD and no esophagitis or BE on endoscopy	Tobacco consumption, alcohol consumption, use of NSAIDs	11	975	Any Length BE
Chacaltana et al[35] (2009) 1b	2009	Case Control	Peru	Patients participating in a gastric cancer screening campaign, with histologically confirmed BE	Patients participating in a gastric cancer screening campaign, with diagnosed GERD	Tobacco consumption, alcohol consumption, use of NSAIDs	11	975	Any Length BE
Conio et al[36] (2002) 1a	2002	Case Control	Italy	Patients referred for upper gastrointestinal endoscopy, with histologically confirmed BE	Patients admitted to hospitals in the same catchment areas as the cases for acute, non-neoplastic, non-GI conditions	None	109	457	SSBE
Conio et al[36] (2002) 1b	2002	Case Control	Italy	Patients referred for upper gastrointestinal endoscopy, with histologically confirmed BE	Patients admitted to hospitals in the same catchment areas as the cases for acute, non-neoplastic, non-GI conditions	None	40	457	LSBE
Conio et al[36] (2002) 1c	2002	Case Control	Italy	Patients referred for upper gastrointestinal endoscopy, with histologically confirmed BE	Patients admitted to hospitals in the same catchment areas as the cases for acute, non-neoplastic, non-GI conditions	Center, gender and age	149	457	Any Length BE
Conio et al[36] (2002) 1d	2002	Case Control	Italy	Patients referred for upper gastrointestinal endoscopy, with histologically	GERD controls	Center, gender and age	149	457	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
				confirmed BE					
Dickman et al[23] (2010)	2010	Cross-sectional	Israel	Consecutive endoscopy cases with histologically confirmed BE	Consecutive endoscopy cases without histologically confirmed BE	Gender	64	166	Any Length BE
Grassi et al[37] (2006)	2006	Cross-sectional	Italy	Outpatients referred for endoscopy, with histologically confirmed BE	Outpatients referred for endoscopy, without histologically confirmed BE	None	47	224	SSBE
Jonaitis et al[38] (2011)	2011	Cross-sectional	Lithuania	Consecutive patients aged 18 years and over referred for upper endoscopy from primary and secondary settings due to upper GI and/or “alarm” symptoms, with histologically confirmed BE	Consecutive patients aged 18 years and over referred for upper endoscopy from primary and secondary settings due to upper GI and/or “alarm” symptoms, without histologically confirmed BE	Ulcer and/or stricture of esophagus, age, smoking (>10 cigarettes per day), H. pylori status, BMI, male gender	33	4032	Any Length BE
Kuo et al[39] (2009)	2009	Cross-sectional	Taiwan	Consecutive patients who underwent upper endoscopy for a variety of GI, with histologically confirmed BE	Consecutive patients who underwent upper endoscopy for a variety of GI, without histologically confirmed BE	Gender, age, GERD duration, smoking history, alcohol use, BMI, the presence of erosive esophagitis	13	736	Any Length BE
Lee et al[40] (2010)	2010	Cross-sectional	Korea	BE patients who had visited outpatient clinics to receive an upper GI endoscopy and who had clinical symptoms	Patients without BE who had visited outpatient clinics to receive an upper GI endoscopy and who had clinical symptoms	None	21	2048	Any Length BE
Lord et al[41](2008)	2008	Cross-sectional	USA	Patients with symptoms suggestive of reflux, with histologically confirmed BE	Patients with symptoms suggestive of reflux, without histologically confirmed BE	None	44	160	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Mathew et al[42] (2011)	2011	Cross-sectional	India	Consecutive GERD patients with histologically confirmed BE	Consecutive GERD patients without histologically confirmed BE	Age, duration of symptoms, presence of dysphagia, presence of eructation	25	278	Any Length BE
Moons et al[43](2008)	2008	Case Control	The Netherlands	Caucasian patients referred for the evaluation of reflux-related symptoms, odynophagia or dysphagia, suspected extra-esophageal manifestations of GERD, with histologically confirmed BE	Caucasian patients referred for the evaluation of reflux-related symptoms, odynophagia or dysphagia, suspected extra-esophageal manifestations of GERD, without histologically confirmed BE	Age, gender, tested cytokine polymorphisms	255	502	Any Length BE
Nasseri-Moghaddam et al[44] (2003) 1a	2003	Cross-sectional	Iran	All patients 18 years of age and older scheduled for upper GI endoscopy with histologically confirmed BE	All patients 18 years of age and older scheduled for upper GI endoscopy without histologically confirmed BE	None	45	269	SSBE
Nasseri-Moghaddam et al[44] (2003) 1b	2003	Cross-sectional	Iran	All patients 18 years of age and older scheduled for upper GI endoscopy with histologically confirmed BE	All patients 18 years of age and older scheduled for upper GI endoscopy without histologically confirmed BE	None	8	269	LSBE
Nasseri-Moghaddam et al[44] (2003) 1c	2003	Cross-sectional	Iran	All patients 18 years of age and older scheduled for upper GI endoscopy with histologically confirmed BE	All patients 18 years of age and older scheduled for upper GI endoscopy without histologically confirmed BE	None	68	269	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Oberg et al[45] (1998) 1a	1998	Cross-sectional	USA	Patients with symptoms of foregut disease and no previous history of gastric or esophageal surgery, with histologically confirmed BE	Patients with symptoms of foregut disease and no previous history of gastric or esophageal surgery, without histologically confirmed BE	None	30	262	SSBE
Oberg et al[45] (1998) 1b	1998	Cross-sectional	USA	Patients with symptoms of foregut disease and no previous history of gastric or esophageal surgery, with histologically confirmed BE	Patients with symptoms of foregut disease and no previous history of gastric or esophageal surgery, without histologically confirmed BE	None	32	262	LSBE
Oberg et al[45] (1998) 1c	1998	Cross-sectional	USA	Patients with symptoms of foregut disease and no previous history of gastric or esophageal surgery, with histologically confirmed BE	Patients with symptoms of foregut disease and no previous history of gastric or esophageal surgery, without histologically confirmed BE	None	62	262	LSBE
Odemis et al[46] (2009)	2009	Cross-sectional	Turkey	Consecutive patients referred for endoscopy for any clinical indication, with histologically confirmed BE	Consecutive patients referred for endoscopy for any clinical indication, without histologically confirmed BE	None	12	1000	Any Length BE
Peng et al[47] (2009)	2009	Cross-sectional	China	Consecutive individuals aged 18-75 who underwent routine upper endoscopy as part of their regular medical examination, with histologically confirmed BE	Consecutive individuals aged 18-75 who underwent routine upper endoscopy as part of their regular medical examination, without histologically confirmed BE	Reflux symptoms, alcohol consumption	27	2580	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
Rajendra et al[48] (2004)	2004	Cross-sectional	Malaysia	Consecutive patients undergoing elective gastroscopy for predominantly upper abdominal or reflux complaints, with histologically confirmed BE	Consecutive patients undergoing elective gastroscopy for predominantly upper abdominal or reflux complaints, without histologically confirmed BE	None	123	1985	Any Length BE
Rajendra et al[49] (2007) 1a	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	GERD and non-GERD controls combined	None	25	188	LSBE
Rajendra et al[49] (2007) 1b	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	GERD and non-GERD controls combined	None	25	188	SSBE
Rajendra et al[49] (2007) 1c	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	GERD and non-GERD controls combined	None	30	188	Any Length BE
Rajendra et al[49] (2007) 1d	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	GERD controls	None	25	188	LSBE
Rajendra et al[49] (2007) 1e	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	GERD controls	None	25	188	SSBE
Rajendra et al[49] (2007) 1f	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	GERD controls	None	30	188	Any Length BE
Rajendra et al[49] (2007) 1g	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	Non-GERD controls - patients without histologically confirmed BE undergoing upper GI endoscopy for	None	25	188	LSBE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
					reasons other than reflux symptoms, BE surveillance, or any form of dyspepsia				
Rajendra et al[49] (2007) 1h	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	Non-GERD controls - patients without histologically confirmed BE undergoing upper GI endoscopy for reasons other than reflux symptoms, BE surveillance, or any form of dyspepsia	None	25	188	SSBE
Rajendra et al[49] (2007) 1i	2007	Cross-sectional	Malaysia	Patients referred to endoscopy unit, found to have histologically confirmed BE	Non-GERD controls - patients without histologically confirmed BE undergoing upper GI endoscopy for reasons other than reflux symptoms, BE surveillance, for any form of dyspepsia	None	30	188	Any Length BE
Ringhofer et al[50](2008)	2008	Cross-sectional	Austria	Patients investigated for symptoms of GERD with histologically confirmed BE	Patients investigated for symptoms of GERD without histologically confirmed BE	None	19	102	Any Length BE
Sarr et al[51] (1985)	1985	Cross-sectional	USA	Patients investigated for symptoms compatible with GERD, including regurgitation, heartburn, epigastric distress, and dysphagia, with histologically confirmed BE	Patients investigated for symptoms compatible with GERD, including regurgitation, heartburn, epigastric distress, and dysphagia, without histologically confirmed BE	None	44	362	Any Length BE
Sgouros et al[52](2007) 1a	2007	Case Control	Greece	Patients aged 18-79 who presented to the clinic for investigation of heartburn and/or	Patients with an endoscopic diagnosis of peptic ulcer disease who presented during the same period	None	17	863	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
				acid regurgitation, with histologically confirmed BE	as cases, without symptoms typical of reflux and without BE				
Sgouros et al[52](2007) 1b	2007	Case Control	Greece	Patients aged 18-79 who presented to the clinic for investigation of heartburn and/or acid regurgitation, with histologically confirmed BE	GERD patients without BE	None	17	863	Any Length BE
Sgouros et al[52](2007) 1c	2007	Case Control	Greece	Patients aged 18-79 who presented to the clinic for investigation of heartburn and/or acid regurgitation, with histologically confirmed BE	GERD and non-GERD controls combined	None	17	863	Any Length BE
Toruner et al[53] (2004)	2004	Cross-sectional	Turkey	Consecutive dyspeptic patients, never previously investigated, who were referred for upper endoscopy in whom histologically confirmed BE was found	Consecutive dyspeptic patients, never previously investigated, who were referred for upper endoscopy, without histologically confirmed BE	None	29	395	Any Length BE
Trujillo-Benavides et al[54] (2005)	2005	Cross-sectional	Mexico	Consecutive patients undergoing endoscopy in whom histologically confirmed BE was found	Consecutive patients undergoing endoscopy without histologically confirmed BE	None	10	109	Any Length BE
Van Zanten et al[55] (2006)	2006	Cross-sectional	Canada	Patients >18 years of with a primary complaint of at least 3 months of either	Patients >18 years of with a primary complaint of at least 3 months of either continuous or intermittent	None	25	1040	Any Length BE

Authors	Year	Study	Country	Cases	Controls	Adjusted Variables	Number of Cases	Total Size	Length of
				continuous or intermittent dyspepsia of any severity, with histologically confirmed BE	dyspepsia of any severity, without histologically confirmed BE				
Wang et al[56] (2008)	2008	Cross-sectional	USA	Patients undergoing an upper endoscopy for any indication, with histologically confirmed BE	Patients undergoing an upper endoscopy for any indication, without histologically confirmed BE	Gender, age, race, length of BE	1215	2511	Any Length BE
Xiong et al[57] (2010)	2010	Cross-sectional	China	Consecutive patients aged 18-88 receiving an endoscopy for upper GI symptoms, with histologically confirmed BE	Consecutive patients aged 18-88 receiving an endoscopy for upper GI symptoms, without histologically confirmed BE	Age, gender, reflux esophagitis, BMI, heartburn	21	2022	Any Length BE
Yilmaz et al[58] (2006)	2006	Cross-sectional	Turkey	Patients who underwent upper endoscopy, , with histologically confirmed BE	Patients who underwent upper endoscopy, , without histologically confirmed BE	None	84	18766	Any Length BE

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; GI, gastrointestinal; LES, lower esophageal sphincter; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2: Meta-analysis by different study characteristics

Factor	SSBE OR (95% CI)	Any Length BE OR (95% CI)	LSBE OR (95% CI)
Control Group			
GERD Controls	1.86 (1.16-2.97)	3.65 (2.74-4.85)	11.17 (6.38-19.55)
Non-GERD Controls	7.93 (2.05-30.59)	13.72 (3.54-53.22)	13.44 (8.26-21.87)
Adjusted ORs			
Adjusted for any variables	-	2.99 (2.24-3.96)	13.70 (9.61-19.54)
Adjusted for BMI	-	2.63 (1.85-3.76)	-
Adjusted for reflux	-	3.35 (2.25-4.39)	13.84 (5.19-36.89)
Not Adjusted	2.85 (1.43-5.67)	4.26 (2.82-6.43)	11.97 (5.53-25.88)
Continent			
Europe	3.40 (0.53-21.89)	7.93 (3.39-18.58)	-
North America	2.82 (2.35-3.37)	3.38 (1.95-5.86)	13.22 (9.63-18.14)
South America	-	12.14 (3.27-45.13)	-
Asia	-	3.84 (2.48-5.94)	-
Study type			
Case control	5.35 (1.74-16.47)	4.38 (2.91-6.61)	13.35 (9.62-18.53)
Cross-sectional	1.96 (1.29-2.99)	3.66 (2.72-4.91)	11.30 (5.06-25.21)

Figure 1: Study Selection Flowchart

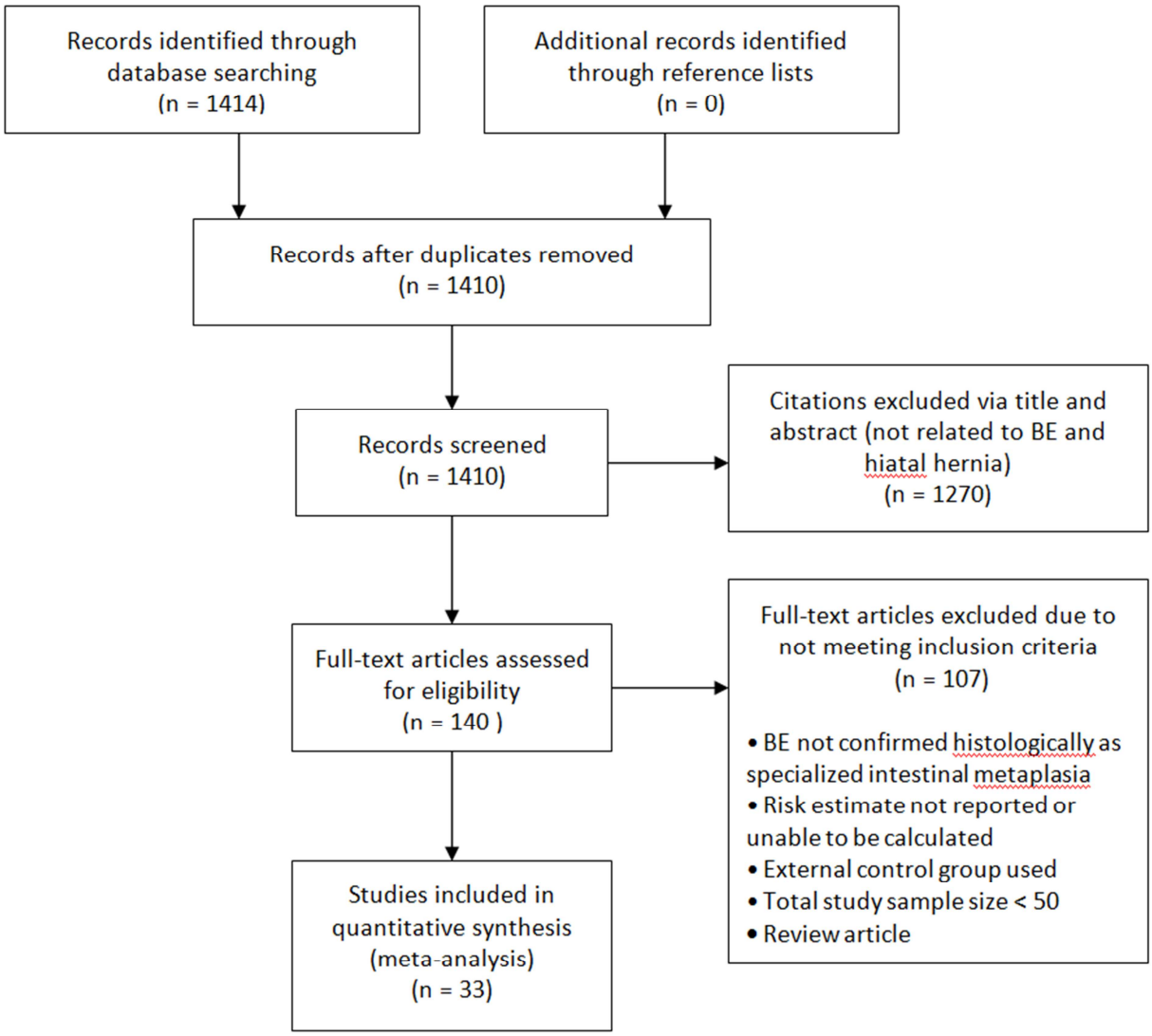
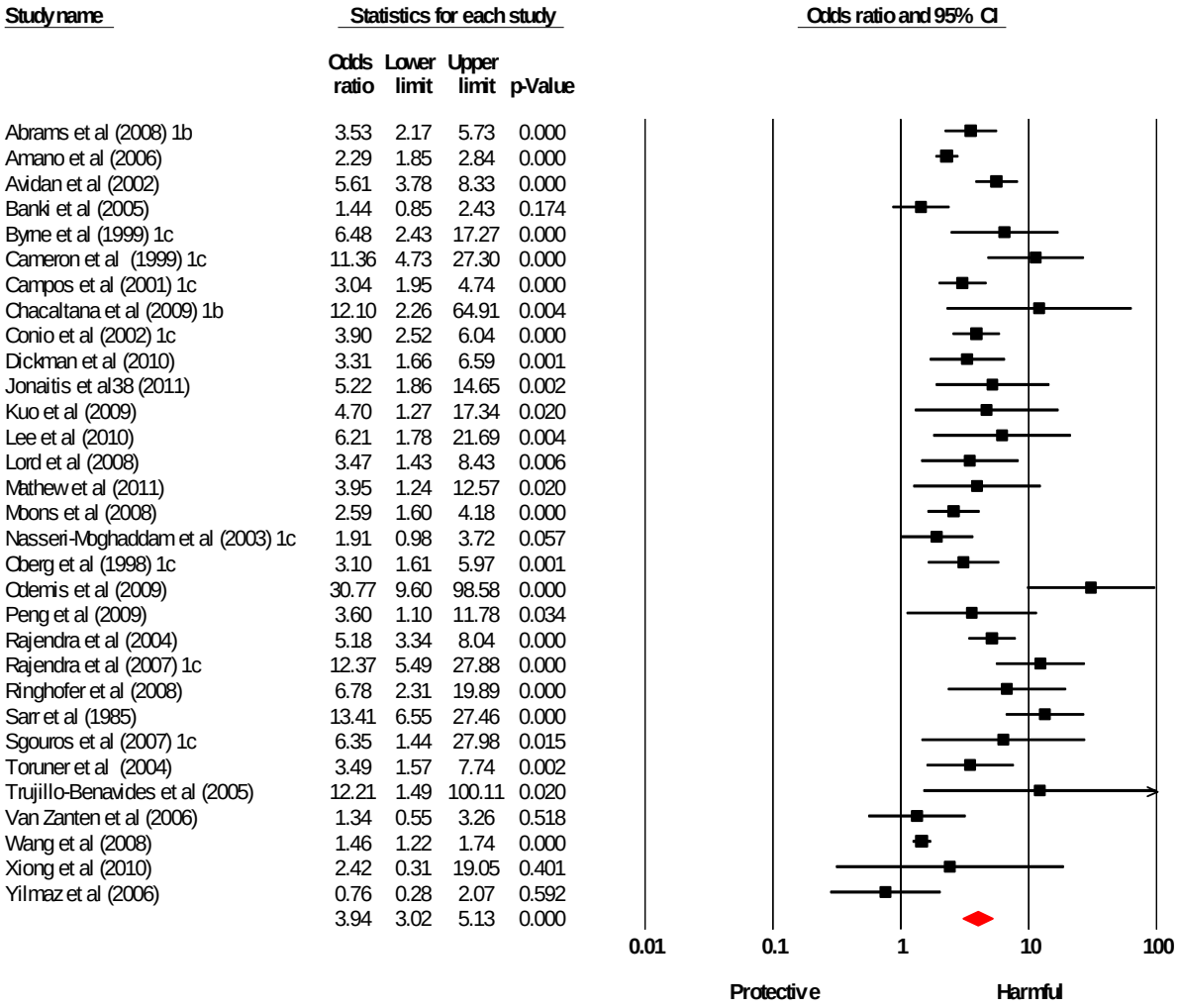


Figure 2: Meta-Analysis of the association between any length Barrett's esophagus and hiatal hernia



Test for heterogeneity I^2=82.03%, p<0.001. Each study is shown by an odds ratio estimate with the corresponding 95% CI.

Figure 3: Funnel plot to assess publication bias

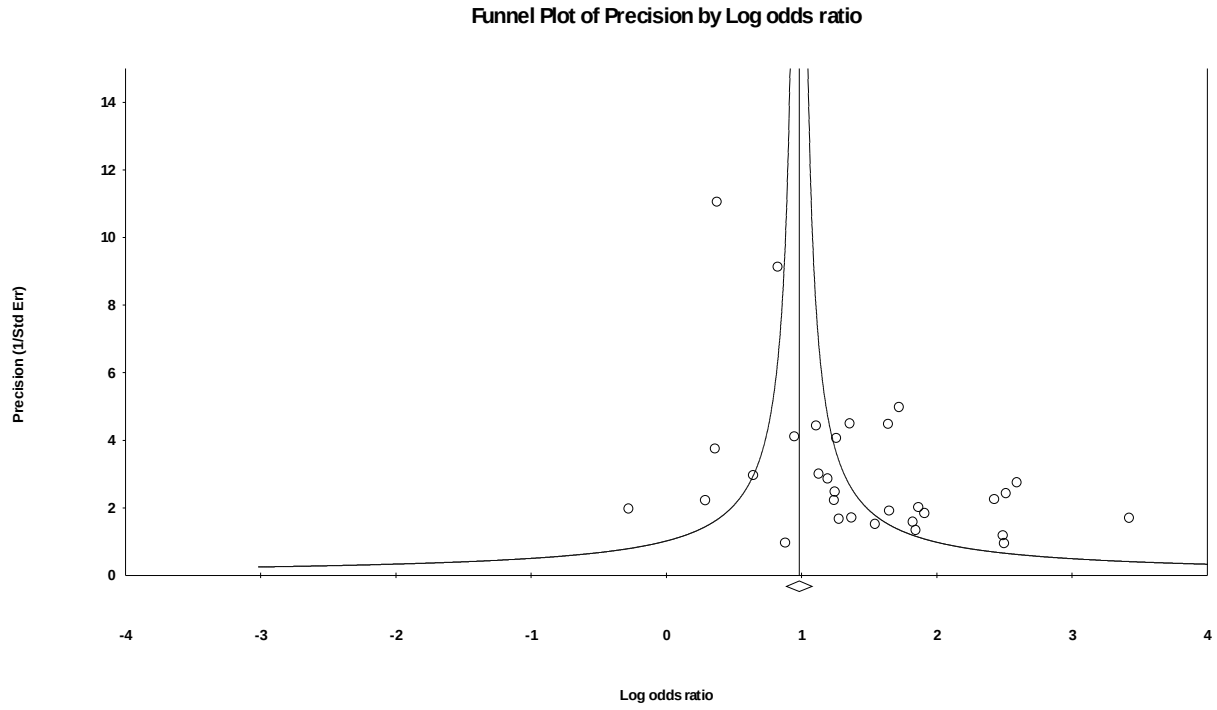
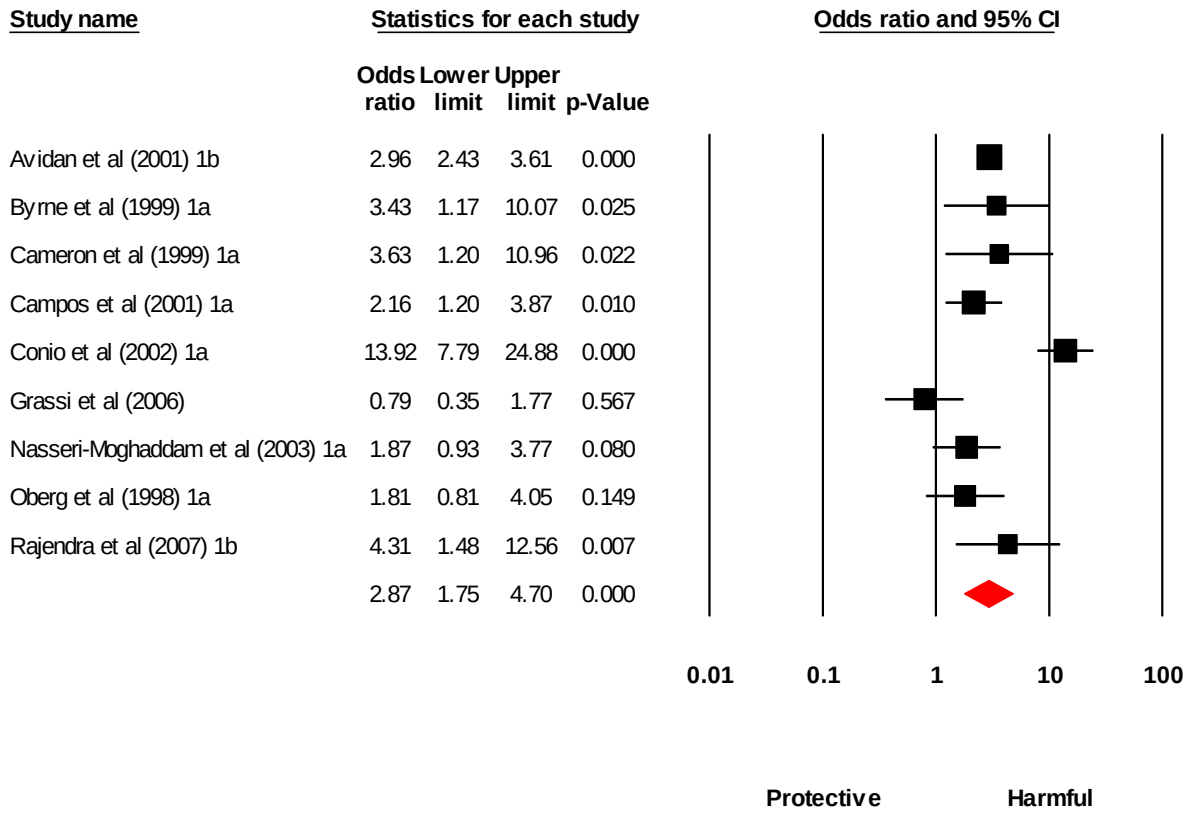
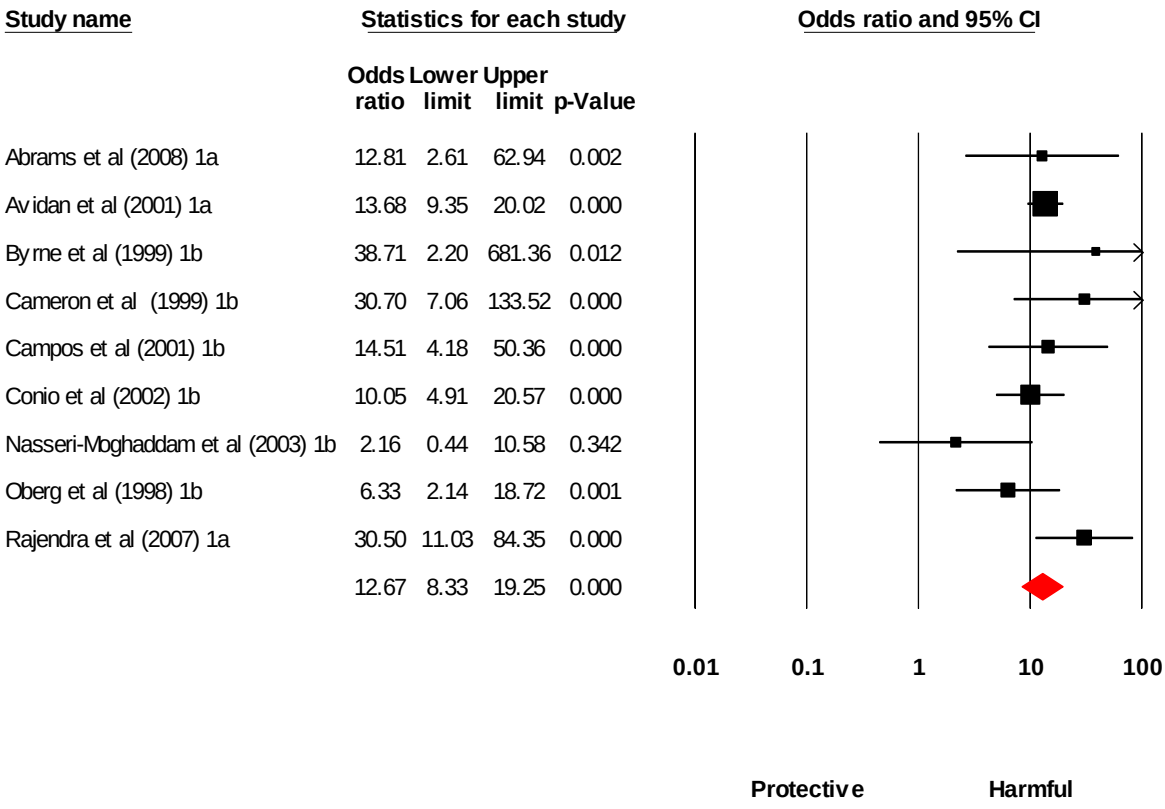


Figure 4: Meta-Analysis of the association between short segment Barrett's esophagus and hiatal hernia



Test for heterogeneity $I^2 = 81.15\%$, $p < 0.001$. Each study is shown by an odds ratio estimate with the corresponding 95% CI.

Figure 5: Meta-Analysis of the association between long segment Barrett's esophagus and hiatal hernia



Test for heterogeneity I^2=31.95%, p = 0.162. Each study is shown by an odds ratio estimate with the corresponding 95% CI.

CHAPTER 3

CIGARETTE SMOKING AND THE RISK OF BARRETT'S ESOPHAGUS

INTRODUCTION

Barrett's Esophagus (BE) involves the replacement of the normal squamousesophageal lining by specialized or intestinal columnar epithelium.[1,2] The main clinical significance of BE is its association with an increased risk of developing esophageal adenocarcinoma,[3] which although historically an uncommon disease, has been experiencing a dramatic increase in incidence in the US and other Western countries over recent decades.[4-7] The prevalence of BE in the general population is uncertain mainly because BE subjects are often asymptomatic and therefore do not present for diagnostic endoscopy. However, a study from Sweden found a prevalence of 1.6% in a random sample of 3000 individuals from the general population.[8] Among patients with gastroesophageal reflux disease (GERD), which is a common complaint, the prevalence of BE has been reported to be between 3 and 15%.[9, 10]

Risk factors for BE include white race, male sex, older age, obesity[11] and GERD.[12] While cigarette smoking is a well-recognized risk factor in the development of esophageal squamous cell carcinoma,[13] and has been associated with esophageal adenocarcinoma in some studies,[14] it has not been definitely linked with an increased risk of developing BE. The literature results are currently mixed, with some studies showing a positive association,[8,11,15-17] while others report no association.[18-22] A recent analysis of 5 case control studies from the International Barrett's and Esophageal Adenocarcinoma Consortium ("BEACON") consortium[23] found a positive relationship between cigarette smoking and BE, thus providing a strong indicator that an association is present.

With a rapidly increasing incidence of adenocarcinoma, which carries a poor

prognosis,[24] the importance of identifying modifiable risk factors for its precursor lesion, BE, is obvious in terms of patient education of preventative measures. To date no meta-analysis of the relationship between cigarette smoking and BE has been performed. To confirm the relationship between smoking and BE found in the recent BEACON consortium analysis,[23] we conducted a meta-analysis combining the results of studies reporting the prevalence of cigarette smoking in BE subjects, and thus provided a quantitative estimate of the increased risk of BE associated with smoking.

MATERIALS AND METHODS

Search strategy

We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines[25] in conducting our meta-analysis. A systematic search was conducted through four electronic databases (Medline [1950 – present], PubMed [1950 – present], Embase [1947 – present], and Current Contents Connect [1998 – present]) to April 18, 2012, for observational studies of BE patients, to identify relevant articles. The terms "Barrett's Esophagus" or "Barrett's esophagus" and "smoking" or "tobacco" or "cigarettes" were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were manually searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed and authors were not contacted for missing data.

Inclusion criteria

Studies were included if they met the following inclusion criteria: (i) studies used a case control, nested case control, cross-sectional or cohort study design; (ii) BE was recognized on endoscopy and confirmed histologically as specialized intestinal metaplasia (SIM); (iii) the prevalence of cigarette smoking in BE cases and controls groups was examined; (iv) the risk point estimate was reported as an odds ratio (OR), or the data was presented such that an odds ratio could be calculated; (v) the 95% confidence interval (CI) was reported, or the data was presented such that the confidence interval could be calculated; (vi) an internal control group was used when calculating the risk estimate.

We excluded studies that did not meet the inclusion criteria. Specifically, studies were excluded for the following reasons: (i) studies looked at endoscopically-suspected BE patients, and not subjects with SIM;[26-30] (ii) data on prevalence of smoking in BE cases and controls not reported;[31,32] (iii) article was part of a cohort study from which more recent, updated data was available;[33] (iv) study used endoscopically-suspected BE subjects as controls.[34] Studies were included or excluded following consensus between two authors (J.A. and G.E.).

Data extraction

We performed the data extraction via a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction (prospective or retrospective), control groups

used, country, continent, case control matching, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, confidence intervals or data used to calculate confidence intervals, smoking status (current, former or ever smoker), the number of pack-years smoked, and length of BE. We selected only subjects with SIM to serve as the BE cases in our analysis; if different sub-groups were reported, such as endoscopically suspected non-SIM BE patients and SIM BE patients, only the SIM BE patient data was used. Where BE length was not stated, the study was categorized as "any length BE". Adjusted ratios were extracted in preference to non adjusted ratios, however, where ratios were not provided, unadjusted odds ratios and confidence intervals were calculated. Where more than one adjusted ratio was reported, the ratio with the highest number of adjusted variables was selected. Where multiple risk estimates were available in the same study, for example when risk estimates were reported for different control groups, they were included as separate risk estimates. The different risk estimates from the same study were denoted by the study name followed by sequential alphabetical letters. For example, the study by Anderson et al[18] provided risk estimates for ever smokers, former smokers, current smokers, smoking < 15 pack years, and smoking > 40 pack years. These different risk estimates were referred to in the tables as Anderson et al a[18], Anderson et al b[18], Anderson et al c[18] , Anderson et al d[18] and Anderson et al e[18], respectively. We excluded data on subjects who smoked pipe, cigar or chewed tobacco, so as to better examine the effect on subjects of smoking tobacco in cigarette form, compared to those who did not use tobacco.

Statistical analysis

Pooled odds ratios (OR) and 95% confidence intervals (CI) for the effect of smoking on the risk BE were calculated using a random effects model.[35] Separate risk estimates were calculated comparing BE cases with different control groups, namely a non-GERD control group and a GERD control group. The comparison between BE patients and GERD and non-GERD patients was done for two reasons. Firstly, many of the individual studies themselves used either GERD or non-GERD controls. To eliminate a layer of heterogeneity on the control groups, we maintained this grouping in comparing GERD and non-GERD patients as two separate control groups. Secondly, since GERD is itself a risk factor for BE[12], we wanted to see if there existed a relationship between BE and smoking that was independent of GERD. The non-GERD control group included both population-based controls, as well as subjects who were received an upper endoscopy for any indication, but who were not diagnosed with GERD, or the diagnosis of GERD was not specified. We thus also calculated risk estimates using the sub-set of the non-GERD controls representing population-based controls as the control group. Exposure variables relating to cigarette smoking were ever-smokers, current smokers and former smokers. The smoking exposure was either for current smokers, former smokers, or ever-smokers – the “ever-smoking” group included both current and/or former smokers, and was included as a subgroup analysis to examine if an association between having ever smoked and BE existed, and also to compare this any association found with BE in current smokers and former smokers. From each study that reported pack-years smoked, we grouped all the risk estimates for the lowest reported number of pack years smoked in the "lowest pack-years" group, and the risk estimates for the highest reported number of pack years smoked in the "highest pack-years" group, and calculated pooled ORs and 95% CIs for each of these groups. Due to the smaller number of studies reporting on number of pack-years smoked, these analyses were performed

using the non-GERD and GERD controls together, comparing BE cases with "all controls".

The degree of heterogeneity was quantified using the I2 statistic, which represents the percentage of the total variability across studies which is due to heterogeneity rather than chance alone. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity, respectively.[36] Subgroup analyses by adjustment for confounding variables, study type, length of BE and continent were also performed using the ever-smoking as the exposure variable. Where heterogeneity was present, a sensitivity analysis was performed to determine the influence of each study on the pooled risk estimates by excluding individual studies one at a time.

Publication bias was quantified using the Egger's regression model,[37] and if statistically significant publication bias was detected, the effect of bias was assessed using the fail-safe number method and the trim-and-fill method. The fail-safe number represents the number of studies that we would need to have missed for our observed result to be nullified to statistical non-significance at the $P < 0.05$ level.[38] The trim-and-fill method adjusts for potential unpublished studies in the meta-analysis by calculating new pooled ORs based on a more symmetric funnel plot which are then compared to the original pooled OR. Similarity between the two decreases the likelihood that publication bias significantly affected the meta-analysis results. Results were regarded as statistically significant if the two-tailed $P < 0.05$. All analyses were performed with Comprehensive Meta-analysis (version 2.0).

RESULTS

Search results and study characteristics

From 811 studies initially identified, 39[8,11,15-22,39-67] met our inclusion criteria (Figure 1). Selected characteristics of the included studies are presented in Table 1. The studies represented a variety of geographical regions, with 17 North American studies, 11 European studies, seven Asian studies, two Australian studies, and one study each from Africa and South America. Study sizes ranged from 100 to 27 813, and BE cases ranged from 8 to 1677. Overall, there were 7069 BE patients and 132 168 participants.

Quantitative data synthesis

Table 2 contains the risk estimates calculated for the association of BE with different smoking exposures using the non-GERD, population-based and GERD control groups, as well as the combined "all controls" group as comparisons. 27 studies[8,11,17,18,20-22,39,44,45,47-55,57,60,62-67] comprising 5965 BE cases with a total of 125 534 individuals were included in the meta-analysis for comparing BE cases with non-GERD controls. BE patients were more likely to have ever smoked compared with non-GERD controls (OR 1.44) (Figure 2). There was statistically significant heterogeneity (I^2 = 62%, P = 0.002) and a sensitivity analysis did not identify any one study which contributed significantly to the heterogeneity. The Egger test for publication bias was significant (P = 0.027). The fail-safe number was 122 studies, and the trim-and-fill method showed an imputed risk estimate of OR 1.31 (95% CI, 1.07-1.60). There was also an increased risk of BE associated with being current smoker (OR 1.33) and a former smoker (OR 1.51). In the former smoker analysis, Smith et al[17] was a major contributor to heterogeneity, with the heterogeneity being reduced and becoming statistically insignificant with removal of

the study (I^2 = 49%, P = 0.057), while the pooled risk estimate was only minimally affected (OR 1.40, 95% CI, 1.15-1.72). When stratified by adjustment for any confounding factors, pooled risk estimates of the seven included studies[11,48-50,55,63] revealed that being an ever-smoker was associated with an increased risk of BE (OR 1.90). The heterogeneity became statistically insignificant on sensitivity analysis with the omission of Jacobson et al,[49] (I^2 = 44%, P = 0.111), while the pooled risk estimate was increased (OR 2.13; 95% CI, 1.52-2.98). The sub-group analysis of the six[11,48 50,55] studies which adjusted for measures of obesity showed an increased risk of BE associated with ever smoking (OR 1.72). There was heterogeneity which again was reduced and became statistically insignificant when Jacobson et al[49] was removed (I^2 = 22%, P= 0.273), while the pooled risk estimate was increased (OR 1.91; 95% CI, 1.46-2.51). As Jacobson et al[49] only studied a female population, and so its removal also yielded the risk estimate for stratification by adjustment for age and gender. The sub group analyses by study type, length of BE and continent are shown instable 2.

19 studies[8,11,17,18,20-22,39,40,44,45,47,48,50,53-55,65,67] compared 4829 BE patients with population-based controls, a sub-set of the non-GERD controls. We observed an increased risk of BE associated with being an ever-smoker (OR 1.42), a current smoker (OR 1.22), as well as a former smoker (OR 1.57) when comparing BE subjects with population-based controls. Heterogeneity was present in these analyses and a sensitivity analysis did not reveal any single study which was a significant contributor to the heterogeneity. When stratifying for the four studies[11,48,50,55] which adjusted for any confounding variables, there was an increased risk of BE associated with being an ever-smoker (OR 1.96). The same four studies adjusted for measures of obesity (BMI or waist-to-hip ratio), age and gender, so

no further subgroup analysis was performed. The sub-group analyses by continent are shown in Table 2.

There were 20 studies[15-17,19,21,22,39,41-43,46,54-56,58,59,61-63,67] comprising 3850 BE cases with a total of 40 559 individuals which compared BE cases with GERD controls. We did not observe a statistically significant risk for BE in ever-smokers (Figure 3). However, the risk was increased for current smokers (OR 1.52) and former smokers (OR 1.39). The subgroup analysis of the three studies[16,55,63] which adjusted for any confounding variables showed that ever-smoking was associated with an increased risk of BE, with an OR of 1.96 and high heterogeneity. Rubenstein et al[63] was a significant contributor to the heterogeneity; omitting the study reduced the heterogeneity to a moderate level (I^2 = 57%, P = 0.128), however the pooled risk estimate was likewise affected (OR 1.46; 95% CI, 0.99-2.15). Since Rubenstein et al[63] was also the only one of the three studies which did not adjust for both age and gender, removal of this study resulted in the risk estimate for age and gender-adjustment. The sub-group analyses by continent are shown in Table 2.

Eight studies[11,16-18,48,55,65,67] comprising of 1788 BE cases with a total of 9736 individuals reported an association between the number of pack-years smoked and BE and were included in the dose-response meta-analyses, presented in Table 3. Both lowest and highest pack year groups were associated with an increased risk of BE, the risk being greater for the higher consumption group. A subgroup analysis of the "highest pack-years" group including the six studies[11,16-18,65,67] which adjusted for measure of obesity found a further increase in risk (OR 1.70; 95% CI, 1.37-2.10).

DISCUSSION

Our meta-analysis shows a positive relationship between cigarette smoking and BE, confirming the findings of Cook et al.[23] Our studies used both GERD controls and non-GERD controls as the comparator groups, which enabled us to calculate pooled ORs comparing the risk estimates associated with smoking in BE patients with different control groups. The strongest associations were found when comparing BE patients with population-based controls, and this was true both for the overall analyses, as well as the subgroup analyses. While the associations were positive, the weakest associations between smoking and BE were found when comparing BE patients with GERD controls. This suggests that smoking might be implicated in the etiology of both GERD and BE, and indeed studies have shown that smoking may contribute to gastroesophageal reflux by lowering lower esophageal sphincter tone.[68, 69]

We recognized that our results may be influenced by confounders, and while we have used adjusted ORs when available, some studies did not report adjusted ORs. Sub-group analyses performed for the ever-smokers exposure group found the relationships to increase in strength for all comparator groups when adjusting for confounders. This suggest that the presence of confounders have not biased our overall results.

A stronger relationship with BE was observed in former smokers when compared with current or ever-smokers across all the comparator group analyses. This is interesting, and is something which was noted by other investigators,[11,54,65] who speculated on increased health-seeking behavior among former smokers leading to an increased

likelihood of BE diagnosis, or increased susceptibility of current smokers to acquire Helicobacter pylori,[65] which is thought to be protective of BE,[70] as possible explanations for the phenomenon. To this we add our hypothesis that former smokers may experience weight gain which may in turn increase their risk for developing GERD and BE, and hence the increased risk associated with BE in this exposure group. It has been documented that smoking cessation is often followed by weight gain,[71,72] and that central adiposity and obesity are risk factors for the development of BE.[11] While plausible, this explanation is still speculative in nature, and no established explanation currently exists.

A possible dose response was suggested by our results, with a stronger association found between smoking and BE in the "highest pack-year" group, compared with the "lowest pack-year" group (OR 1.53 versus OR 1.41). Since it has been found that heavy smokers tend to have increased body weight compared with light smokers,[73,74] we conducted a subgroup analysis for the studies in the "highest pack-year" group which adjusted for measures of obesity. The risk was actually increased in the "highest pack-year" group when adjusting for obesity, suggesting that obesity is not confounding the results in the "highest pack-year" group. The presence of a dose response would suggest a real association between smoking and the risk of developing BE, however, there is considerable overlap of the 95% CIs between the lowest and highest pack-year group analyses, and so we cannot comment with confidence about the presence of a trend from lowest to highest levels of consumption.

When stratifying by study design, we observed the positive relationship between smoking and BE to be maintained. While the pooled risk estimate for ever smokers in

the case control subgroup analysis was predictably greater (OR 1.68) than for ever smokers in the cohort subgroup analysis (OR 1.20), the pooled risk estimate for the cohort subgroup analysis was statistically significant and approximated the risk estimates for ever- and current smokers in the main analyses. We therefore concluded that study design was not a significant source of bias in our results. A moderate to high degree of heterogeneity was observed in many of our analyses and often, the source of heterogeneity was not identified on sensitivity analysis. Smith et al[17] was a significant contributor to heterogeneity in the former smokers, BE patients versus non-GERD controls analysis. It was not clear exactly why this study in particular contributed to heterogeneity, though it did have a relatively high proportion of former smokers in the BE group (49%) compared to other studies. Jacobson et al[49] and Rubenstein et al[63] also contributed to heterogeneity in subgroup analyses, and while it was not completely clear as to why this should be, they were the only studies among the studies which adjusted for confounding variables not to adjust for both age and gender. Jacobson et al[49] was based on a female cohort, so this explains their inability to adjust for gender. We thought that one possible explanation for the observed heterogeneity could be the grouping together of different lengths of BE. A minority of studies actually reported risk estimates for SSBE or LSBE, and after we performed subgroup analyses based on BE length, heterogeneity was still present in the LSBE analysis for the ever-smokers exposure group, so this made it less likely that the heterogeneity in the overall analyses being mainly due to the grouping together of BE of differing length. There was insufficient data to calculate a pooled OR for ever-smokers by SSBE. However, since only a few studies reported on BE length, an analysis based on such a small number may not be powered sufficiently to draw solid conclusions from.

Publication bias was present in the analysis for ever-smokers comparing BE patients to non-GERD controls. While the Egger test for publication bias was significant (P = 0.027), the fail-safe number was 122 studies, and given our thorough search strategy, and the fact that the analysis itself only consisted of 27 studies, we thought it unlikely that 122 studies would have been missed. In addition, the trim-and-fill method showed an imputed risk estimate which was statistically significant and similar to our observed risk estimate. We therefore concluded that publication bias existed, but was minimal.

Our study had a number of strengths. The MOOSE guidelines were followed. A thorough search was performed through four databases and we imposed no language restrictions. Studies which used external control groups were excluded. The use of an internal control group is recognized as a more statistically robust way of study design, and the exclusion of studies using external comparators adds rigor to our analysis. This is the first meta-analysis on the association between cigarette smoking and BE, and it combines a 39 studies with 7069 BE patients, making it the largest study on the subject to date. Cook et al[23] have also found a positive relationship between smoking and BE from an analysis of the BEACON data; our results confirm this from an analysis of a larger number of studies, which included two prospective cohort studies.

Our study also had several limitations. It was subject to the bias present in the individual studies and the possible presence of confounders. Most of our studies followed a case control study design, and were therefore subject to recall and selection bias which are inherent to retrospective studies. In this particular instance however, we did not think that recall bias with regards to smoking was a significant bias, as it has been shown that recall of tobacco use is reliable among study participants.[75] The use of

population-based controls in many of the studies also reduced possible selection bias on the results, as population-based controls were chosen at random from established registries or surgery lists. Also, while we identified 39 studies overall and the total number of BE patients was relatively large, our analyses included small studies. Some of these included only eight or 11 BE patients, and it is questionable as to whether they had the statistical power to generate meaningful results. In addition, our analysis only included two prospective cohort studies.

In summary, this meta-analysis has found evidence that smoking is a risk factor for the development of BE. Positive relationships exist between different smoking exposure variables and BE and the association remained, and increased in strength, after adjusting for significant confounders. Since this represents one of the few potentially modifiable risk factors for BE, we believe that it is an important finding in terms of patient counseling and BE prevention.

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Table 1: Barrett's Esophagus Studies included in the Systematic Review

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Anderson et al (2007) a [18]	2007	Case control	Ireland	Non-GERD controls	62.4 for BE cases, 63 for controls	None	Age and gender	224	711	LSBE	Ever smoker
Anderson et al (2007) b [18]	2007	Case control	Ireland	Non-GERD controls	62.4 for BE cases, 63 for controls	Gender, age at interview date, BMI 5 years prior to the interview date, alcohol intake (grams), years of full-time education and job type (manual, non-manual), gastro-esophageal reflux	Age and gender	224	711	LSBE	Former smoker
Anderson et al (2007) c [18]	2007	Case control	Ireland	Non-GERD controls	62.4 for BE cases, 63 for controls	Gender, age at interview date, BMI 5 years prior to the interview date, alcohol intake (grams), years of full-time education and job type (manual, non-manual), gastro-esophageal reflux	Age and gender	224	711	LSBE	Current smoker
Anderson et al (2007) d [18]	2007	Case control	Ireland	Non-GERD controls	62.4 for BE cases, 63 for controls	Gender, age at interview date, BMI 5 years prior to the interview date, alcohol intake (grams), years of full-time education and job type (manual, non-manual), gastro-esophageal reflux	Age and gender	224	711	LSBE	< 15 pack years
Anderson et al (2007) e [18]	2007	Case control	Ireland	Non-GERD controls	62.4 for BE cases, 63 for controls	sex, age at interview date, BMI 5 years prior to the interview date, alcohol intake (grams), years of full-time education and job type (manual, non-manual), gastro-esophageal reflux	Age and gender	224	711	LSBE	> 40 pack years
Avidan et al (2001) a [20]	2001	Case control	USA	Non-GERD controls	61 for BE cases, 59 for controls	Age, gender, ethnicity, alcohol consumption, hiatus hernia, gastric surgery		650	4063	SSBE	Current smoker
Avidan et al (2001) b [20]	2001	Case control	USA	Non-GERD controls	61 for BE cases, 59 for controls	Age, gender, ethnicity, alcohol consumption, hiatus hernia, gastric surgery		366	4063	LSBE	Current smoker
Avidan et al (2002) [15]	2002	Case control	USA	GERD controls	59.3 for BE cases, 57.7 for controls	None		256	485	Any length	Current smoker
Casson et al (2006) a [39]	2006	Case control	Canada	GERD controls		None		125	402	Any length	Ever smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Casson et al (2006) b [39]	2006	Case control	Canada	Non-GERD controls		None		125	402	Any length	Ever smoker
Chacaltana et al (2009) a [21]	2009	Case control	Peru	GERD controls	52.2 for BE cases, 51.3 for controls	None		11	2273	Any length	Current smoker
Chacaltana et al (2009) b [21]	2009	Case control	Peru	Non-GERD controls	52.2 for BE cases, 50.5 for controls	Hiatal hernia, NSAID consumption, alcohol consumption		11	2273	Any length	Current smoker
Conio et al (2002) [40]	2002	Case control	Italy	Non-GERD controls	58.5 for BE cases, 61.1 for controls	Geographic center, gender and age		149	600	Amy length	Current smoker
Dhawan et al (2001) [41]	2001	Cross-sectional	India	GERD controls	47 for BE cases, 36 for controls	None		16	271	Any length	Current smoker
di Martino et al (2007) [42]	2007	Case control	UK	GERD controls	65 for BE cases, 56 for controls	None		200	584	Any length	Ever smoker
Edelstein et al (2007) a [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio	Age and gender	193	404	Any length	Ever smoker
Edelstein et al (2007) b [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio	Age and gender	193	404	Any length	Former smoker
Edelstein et al (2007) c [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio	Age and gender	193	404	Any length	Current smoker
Edelstein et al (2007) d [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio	Age and gender	54	404	LSBE	Ever smoker
Edelstein et al (2007) e [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio	Age and gender	54	404	LSBE	Former smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Edelstein et al (2007) f [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	LSBE	Ever smoker
Edelstein et al (2007) g [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	Any length	< 13.5 pack-years
Edelstein et al (2007) h [11]	2007	Case control	USA	Non-GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	Any length	> 13.5 pack-years
Edelstein et al (2007) i [11]	2007	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	Any length	< 13.5 pack-years
Edelstein et al (2007) j [11]	2007	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	Any length	> 13.5 pack-years
Edelstein et al (2009) a [16]	2009	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	Any length	Former smoker
Edelstein et al (2009) b [16]	2009	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	193	611	Any length	Current smoker
Edelstein et al (2009) c [16]	2009	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	54	611	LSBE	Ever smoker
Edelstein et al (2009) d [16]	2009	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	54	611	LSBE	Former smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Edelstein et al (2009) e [16]	2009	Case control	USA	GERD controls		Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	54	611	LSBE	Current smoker
Eloubeidi et al (2001) [43]	2001	Case control	USA	GERD controls	64 for BE cases, 57 for controls	None	Age and gender	88	176	Any length	Current smoker
Ferrandez et al (2006) a [44]	2006	Case control	Spain	Non-GERD controls	53.96 for BE cases, 53.37 for controls	None	Age and gender	104	317	Any length	Current smoker
Ferrandez et al (2006) b [44]	2006	Case control	Spain	Non-GERD controls	53.96 for BE cases, 53.37 for controls	None	Age and gender	104	317	Any length	Ex-smoker
Ferrandez et al (2006) c [44]	2006	Case control	Spain	Non-GERD controls	53.96 for BE cases, 53.37 for controls	Age, gender, waist-to-hip ratio, and clinic	month of biopsy and clinic	104	317	Any length	Ever smoker
Fouad et al (2009) [19]	2009	Case control	Egypt	GERD controls	48.3 for BE cases, 37.6 for controls	None		73	1000	Any length	Current smoker
Gerson et al (2002) a [45]	2002	Case control	USA	Non-GERD controls	61	None		27	110	Any length	Current smoker
Gerson et al (2002) b [45]	2002	Case control	USA	Non-GERD controls	61	None		27	110	Any length	Ex-smoker > 10 pack years
Gerson et al (2007) [46]	2007	Case control	USA	GERD controls	58.5 for BE cases, 54.5 for controls	Age, gender, race, GERD duration, income level, alcohol consumption, family history		165	751	Any length	Current smoker
Gerson et al (2009) [47]	2009	Cross-sectional	USA	Non-GERD controls	60 for BE cases, 49 for controls	None		8	126	Any length	Current smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Ibiebele et al (2011) a [48]	2011	Case control	Australia	Non-GERD controls		Age, gender, education, BMI 1 year previously, frequency of heartburn or acid reflux 10 years prior to diagnosis, lifetime alcohol intake, NSAID use, and total energy intake	Age and gender	266	944	Any length	Ever smoker
Ibiebele et al (2011) b [48]	2011	Case control	Australia	Non-GERD controls		Age, gender, education, BMI 1 year previously, frequency of heartburn or acid reflux 10 years prior to diagnosis, lifetime alcohol intake, NSAID use, and total energy intake	Age and gender	266	944	Any length	< 14.9 pack-years
Ibiebele et al (2011) c [48]	2011	Case control	Australia	Non-GERD controls		Age, gender, education, BMI 1 year previously, frequency of heartburn or acid reflux 10 years prior to diagnosis, lifetime alcohol intake, NSAID use, and total energy intake	Age and gender	266	944	Any length	≥ 30 pack-years
Jacobson et al (2011) a [49]	2011	Cohort	USA	Non-GERD controls		Year of endoscopy, age, BMI, physical activity, daily caloric intake/day, alcohol consumption, hormone use		377	20863	Any length	Ever smoker
Jacobson et al (2011) b [49]	2011	Cohort	USA	Non-GERD controls		Year of endoscopy, age, BMI, physical activity, daily caloric intake/day, alcohol consumption, hormone use		377	20863	Any length	Former smoker
Jacobson et al (2011) c [49]	2011	Cohort	USA	Non-GERD controls		Year of endoscopy, age, BMI, physical activity, daily caloric intake/day, alcohol consumption, hormone use		377	20863	Any length	Current smoker
Johansson et al (2007) a [50]	2007	Case control	Sweden	Non-GERD controls	60.3 for BE cases, 51.4 for controls	Age, gender, reflux symptoms, BMI, H.pylori status, alcohol consumption		21	764	Any length	Ever smoker
Johansson et al (2007) b [50]	2007	Case control	Sweden	Non-GERD controls	60.3 for BE cases, 61.8 for controls	Age, gender, reflux symptoms, BMI, H.pylori status, alcohol consumption	Age and gender	21	764	Any length	Ever smoker
Johnston et al (1996) [51]	1996	Cross-sectional	USA	Non-GERD controls	52 for BE cases, 48 for controls	None		16	170	Any length	Current smoker
Jonaitis et al (2011) [52]	2011	Case control	Lithuania	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Ulcer and/or stricture of esophagus, age, hiatal hernia, H. Pylori status, BMI, gender		33	4032	Any length	Current smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Kicinski et al (2009) a [53]	2009	Case control	Poland	Non-GERD controls	55.9 for BE cases, 54.3 for controls	None		36	111	Any length	Current smoker
Kicinski et al (2009) b [53]	2009	Case control	Poland	Non-GERD controls	55.9 for BE cases, 54.2 for controls	None		36	111	Any length	Current smoker
Kubo et al (2009) 1a [54]	2009	Case control	USA	GERD controls	62.7 for BE cases, 45.13 for the total population	Age, race (white vs non-white), gender, location of diagnosis, fruit and vegetable intake, H.pylori status, income, and education	Gender, age and geographical region	320	953	Any length	Former smoker
Kubo et al (2009) 1b [54]	2009	Case control	USA	GERD controls	62.7 for BE cases, 45.13 for the total population	Age, race (white vs non-white), gender, location of diagnosis, fruit and vegetable intake, H.pylori status, income, and education	Gender, age and geographical region	320	953	Any length	Current smoker
Kubo et al (2009) 1c [54]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Age, race (white vs non-white), gender, location of diagnosis, fruit and vegetable intake, H.pylori status, income, and education	Gender, age and geographical region	320	953	Any length	Former smoker
Kubo et al (2009) 1d [54]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Age, race (white vs non-white), gender, location of diagnosis, fruit and vegetable intake, H.pylori status, income, and education	Gender, age and geographical region	320	953	Any length	Current smoker
Kubo et al (2009) 2a [55]	2009	Case control	USA	GERD controls	62.7 for BE cases, 45.13 for the total population	Age, race (white vs. non-white), gender, and education	Gender, age and geographical region	320	953	Any length	Ever vs never
Kubo et al (2009) 2b [55]	2009	Case control	USA	GERD controls	62.7 for BE cases, 45.13 for the total	Age, race (white vs. non-white), gender, and education	Gender, age and geographical	320	953	Any length	Current smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
					population		region				
Kubo et al (2009) 2c [55]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Age, race, gender, and education, BMI, recent alcohol use (number of drinks/week), aspirin or NSAID use, total caloric intake, a comorbidity index (the DxCg score), H. pylori status, geographic location	Gender, age and geographical region	320	953	Any length	Ever smoker
Kubo et al (2009) 2d [55]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population		Gender, age and geographical region	320	953	Any length	Current smoker
Kubo et al (2009) 2e [55]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Age, gender, race, and education	Gender, age and geographical region	320	953	LSBE	Ever smoker
Kubo et al (2009) 2f [55]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Age, gender, race, and education	Gender, age and geographical region	320	953	SSBE	Ever smoker
Kubo et al (2009) 2g [55]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total population	Age, gender, race, and education	Gender, age and geographical region	320	953	Any length	< 10 pack-years
Kubo et al (2009) 2h [55]	2009	Case control	USA	GERD controls	62.7 for BE cases, 45.13 for the total population	Age, gender, race, and education	Gender, age and geographical region	320	953	Any length	< 10 pack-years
Kubo et al (2009) 2i [55]	2009	Case control	USA	Non-GERD controls	62.7 for BE cases, 45.13 for the total	Age, gender, race, and education	Gender, age and geographical	320	953	Any length	> 50 pack-years

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
					population		region				
Kubo et al (2009) 2j [55]	2009	Case control	USA	GERD controls	62.7 for BE cases, 45.13 for the total population	Age, gender, race, and education	Gender, age and geographical region	320	953	Any length	> 50 pack-years
Kuo et al (2010) [56]	2010	Cross-sectional	Taiwan	GERD controls	49.2 for BE cases, 50.5 for the total population	Age, gender, duration of GERD, hiatal hernia, reflux esophagitis, alcohol consumption, BMI		13	736	Any length	Current smoker
Lam et al (2008) [57]	2008	Case control	USA	Non-GERD controls	55 for BE cases, 55 for controls	Age, gender, ethnicity, alcohol consumption		56	5293	Any length	Current smoker
Mathew et al (2011) [58]	2011	Case control	India	GERD controls	50.04 for BE cases,	None		25	303	Any length	Current smoker
Olliver et al (2005) [59]	2005	Case control	UK	GERD controls	63 for BE cases, 52 for controls	None		50	147	Any length	Ever smoker
Park et al (2009) [60]	2009	Cross-sectional	South Korea	Non-GERD controls		Age, gender, NSAID use, BMI, hiatal hernia, cholesterol, alcohol consumption, reflux esophagitis		215	23565	Any length	Current smoker
Rajendra et al (2004) [61]	2004	Case Control	Malaysia	GERD controls	51.1 for BE cases, 60.6 for controls	None		123	1985	Any length	Current smoker
Rajendra et al (2007) a [62]	2007	Case control	Malaysia	GERD controls	55.1 for BE cases, 52.7 for controls	None		25	188	SSBE	Current smoker
Rajendra et al (2007) b [62]	2007	Case control	Malaysia	GERD controls	58.7 for BE cases. 52.7 for controls	None		30	188	LSBE	Current smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Rajendra et al (2007) c [62]	2007	Case control	Malaysia	GERD controls		None		55	188	Any length	Current smoker
Rajendra et al (2007) d [62]	2007	Case control	Malaysia	Non-GERD controls	55.1 for BE cases, 50.6 for controls	None		25	188	SSBE	Current smoker
Rajendra et al (2007) e [62]	2007	Case control	Malaysia	Non-GERD controls	58.7 for BE cases, 50.6 for controls	None		30	188	LSBE	Current smoker
Rajendra et al (2007) f [62]	2007	Case control	Malaysia	Non-GERD controls		None		55	188	Any length	Current smoker
Ronkainen et al (2005) a [8]	2005	Cross-sectional	Sweden	Non-GERD controls	56.9 for BE cases, 53.5 for controls	Age and gender		16	1000	Any length	Current smoker
Ronkainen et al (2005) b [8]	2005	Cross-sectional	Sweden	Non-GERD controls	56 for BE cases, 53.5 for controls	Age and gender		11	1000	SSBE	Current smoker
Rubenstein et al (2008) a [63]	2008	Case control	USA	GERD controls	60 for BE cases, 60 for controls	Age and veteran/civilian status	Age and veteran/civilian status	45	100	Any length	Ever smoker
Rubenstein et al (2008) b [63]	2008	Case control	USA	Non-GERD controls	60 for BE cases, 60 for controls	Age and veteran/civilian status	Age and veteran/civilian status	50	100	Any length	Ever smoker
Siersema et al (2006) [64]	2006	Case control	USA	Non-GERD controls	66 for BE cases, 64 for controls	None		268	536	Any length	Current smoker
Smith et al (2009) a [17]	2009	Case control	Australia	GERD controls	58.2 for BE cases, 53.5 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis		285	1350	Any length	Former smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Smith et al (2009) b [17]	2009	Case control	Australia	GERD controls	58.2 for BE cases, 53.5 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis		285	1350	Any length	Current smoker
Smith et al (2009) c [17]	2009	Case control	Australia	Non-GERD controls	58.2 for BE cases, 57.9 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis	Age and gender	285	1350	Any length	Former smoker
Smith et al (2009) d [17]	2009	Case control	Australia	Non-GERD controls	58.2 for BE cases, 57.9 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis	Age and gender	285	1350	Any length	Current smoker
Smith et al (2009) e [17]	2009	Case control	Australia	Non-GERD controls	58.2 for BE cases, 57.9 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis	Age and gender	285	1350	Any length	< 5 pack years
Smith et al (2009) f [17]	2009	Case control	Australia	GERD controls	58.2 for BE cases, 57.9 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis	Age and gender	285	1350	Any length	< 5 pack years
Smith et al (2009) g [17]	2009	Case control	Australia	Non-GERD controls	58.2 for BE cases, 57.9 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis	Age and gender	285	1350	Any length	≥ 30 pack years
Smith et al (2009) h [17]	2009	Case control	Australia	GERD controls	58.2 for BE cases, 57.9 for controls	Age, gender, education, current BMI, mean alcohol consumption, frequency of aspirin use in the 5 years before diagnosis, frequency of gastroesophageal reflux symptoms 10 years before diagnosis	Age and gender	285	1350	Any length	≥ 30 pack years
Solaymani-Dodaran et al (2004) a [22]	2004	Cross-sectional	UK	GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Ever smoker
Solaymani-Dodaran et al (2004) b [22]	2004	Cross-sectional	UK	GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Current smoker

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Solaymani-Dodaran et al (2004) c [22]	2004	Cross-sectional	UK	GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Former smoker
Solaymani-Dodaran et al (2004) d [22]	2004	Cross-sectional	UK	GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Current smoker
Solaymani-Dodaran et al (2004) e [22]	2004	Cross-sectional	UK	Non-GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Ever smoker
Solaymani-Dodaran et al (2004) f [22]	2004	Cross-sectional	UK	Non-GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Current smoker
Solaymani-Dodaran et al (2004) g [22]	2004	Cross-sectional	UK	Non-GERD controls		None	Age, gender, GP practice	1677	27813	Any length	Former smoker
Steevens et al (2010) a [65]	2010	Cohort	The Netherlands	Non-GERD controls	61.1 for BE cases, 61.3 for controls	None		370	4736	Any length	Ever smoker
Steevens et al (2010) b [65]	2010	Cohort	The Netherlands	Non-GERD controls	61.1 for BE cases, 61.3 for controls	Age, alcohol consumption, and BMI		370	4736	Any length	Former smoker
Steevens et al (2010) c [65]	2010	Cohort	The Netherlands	Non-GERD controls	61.1 for BE cases, 61.3 for controls	Age, alcohol consumption, and BMI		370	4736	Any length	Current smoker
Steevens et al (2010) d [65]	2010	Cohort	The Netherlands	Non-GERD controls	61.1 for BE cases, 61.3 for controls	Age, alcohol consumption, and BMI		370	4736	Any length	< 20 pack years

Authors	Year	Study Type	Country	Controls	Mean Age	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Length of BE	Cigarette smoking exposure
Steevens et al (2010) e [65]	2010	Cohort	The Netherlands	Non-GERD controls	61.1 for BE cases, 61.3 for controls	Age, alcohol consumption, and BMI		370	4736	Any length	≥ 40 pack years
Tseng et al (2008) [66]	2008	Cross-sectional	Taiwan	Non-GERD controls	61.6 for BE cases, 51.7 for controls	None		12	19812	Any length	Current smoker
Veugelers et al (2006) a [67]	2006	Case control	Canada	GERD controls	59 for BE cases, 55 for controls	None		130	431	Any length	Ever smoker
Veugelers et al (2006) b [67]	2006	Case control	Canada	Non-GERD controls	59 for BE cases, 57 for controls	None	Age and gender	130	431	Any length	Ever smoker
Veugelers et al (2006) c [67]	2006	Case control	Canada	Non-GERD controls	59 for BE cases, 57 for controls	None	Age and gender	130	431	Any length	< 5000 lifetime packs of cigarettes
Veugelers et al (2006) d [67]	2006	Case control	Canada	Non-GERD controls	59 for BE cases, 57 for controls	None	Age and gender	130	431	Any length	≥ 5000 lifetime packs of cigarettes

Abbreviations: BE, Barrett's esophagus; BMI, body mass index; GERD, gastroesophageal reflux disease; GI, gastrointestinal; LSBE, long segment Barrett's esophagus; NSAIDs, non-steroidal anti-inflammatory drugs; SSBE, short segment Barrett's esophagus.

Table 2: Meta-Analysis by Different Study characteristics

		Non-GERD controls (including population-based controls)				Population-based controls					GERD controls				
Study Characteristic	**Studies, *n***	**OR (95% CI)**	***P*$_{difference}$**	**I^2, %**	***P*$_{heterogeneity}$**	**Studies, *n***	**OR (95% CI)**	***P*$_{difference}$**	**I^2, %**	***P*$_{heterogeneity}$**	**Studies, *n***	**OR (95% CI)**	***P*$_{difference}$**	**I^2, %**	***P*$_{heterogeneity}$**
Smoking exposure															
Ever smokers	13	1.44 (1.20, 1.74)	<0.001	62	0.002	10	1.42 (1.15, 1.76)	0.001	61	0.006	8	1.18 (0.75, 1.86)	0.474	86	<0.001
Current smokers	26	1.33 (1.14, 1.56)	<0.001	59	<0.001	17	1.22 (1.02, 1.45)	0.030	59	0.001	15	1.52 (1.31, 1.77)	<0.001	0	0.513
Former smokers	9	1.51 (1.21, 1.88)	<0.001	61	0.009	8	1.57 (1.21, 2.05)	0.001	63	0.008	4	1.39 (1.06, 1.81)	0.016	45	0.142
Adjustment for confounders															
Adjustment for any confounders	7	1.90 (1.35, 2.68)	<0.001	71	0.002	4	1.96 (1.41, 2.73)	<0.001	42	0.162	3	1.96 (1.05, 3.64)	0.034	79	0.009
Adjustment for measures of obesity	6	1.72 (1.26, 2.35)	0.001	66	0.01	4	1.96 (1.41, 2.73)	<0.001	42	0.162	-	-	-	-	-

		Non-GERD controls (including population-based controls)				Population-based controls					GERD controls				
Adjustment for age and gender	5	1.91 (1.46, 2.51)	<0.001	22	0.318	4	1.96 (1.41, 2.73)	<0.001	42	0.162	2	1.46 (0.99, 2.15)	0.057	57	0.128
Study Characteristic	**Studies, *n***	**OR (95% CI)**	***P*$_{difference}$**	**I^2, %**	***P*$_{heterogeneity}$**	**Studies, *n***	**OR (95% CI)**	***P*$_{difference}$**	**I^2, %**	***P*$_{heterogeneity}$**	**Studies, *n***	**OR (95% CI)**	***P*$_{difference}$**	**I^2, %**	***P*$_{heterogeneity}$**
Study design															
Case control	10	1.68 (1.28, 2.21)	<0.001	59	0.009	-	-	-	-	-	-	-	-	-	-
Cohort	2	1.20 (1.05, 1.37)	0.008	0	0.935	-	-	-	-	-	-	-	-	-	-
Length of BE															
LSBE	3	1.57 (0.96, 2.57)	0.074	69	0.04	3	1.57 (0.96, 2.57)	0.074	69	0.04	-	-	-	-	-
Continent															
Europe	5	1.44 (1.05, 1.99)	0.025	54	0.069	5	1.29 (0.98, 1.70)	0.071	59	0.045	3	0.84 (0.34, 2.09)	0.706	90	<0.001
North America	6	1.45 (1.09, 1.94)	0.012	56	0.013	4	1.42 (1.04, 1.94)	0.027	47	.128	5	1.40 (0.91, 2.16)	0.123	74	0.005

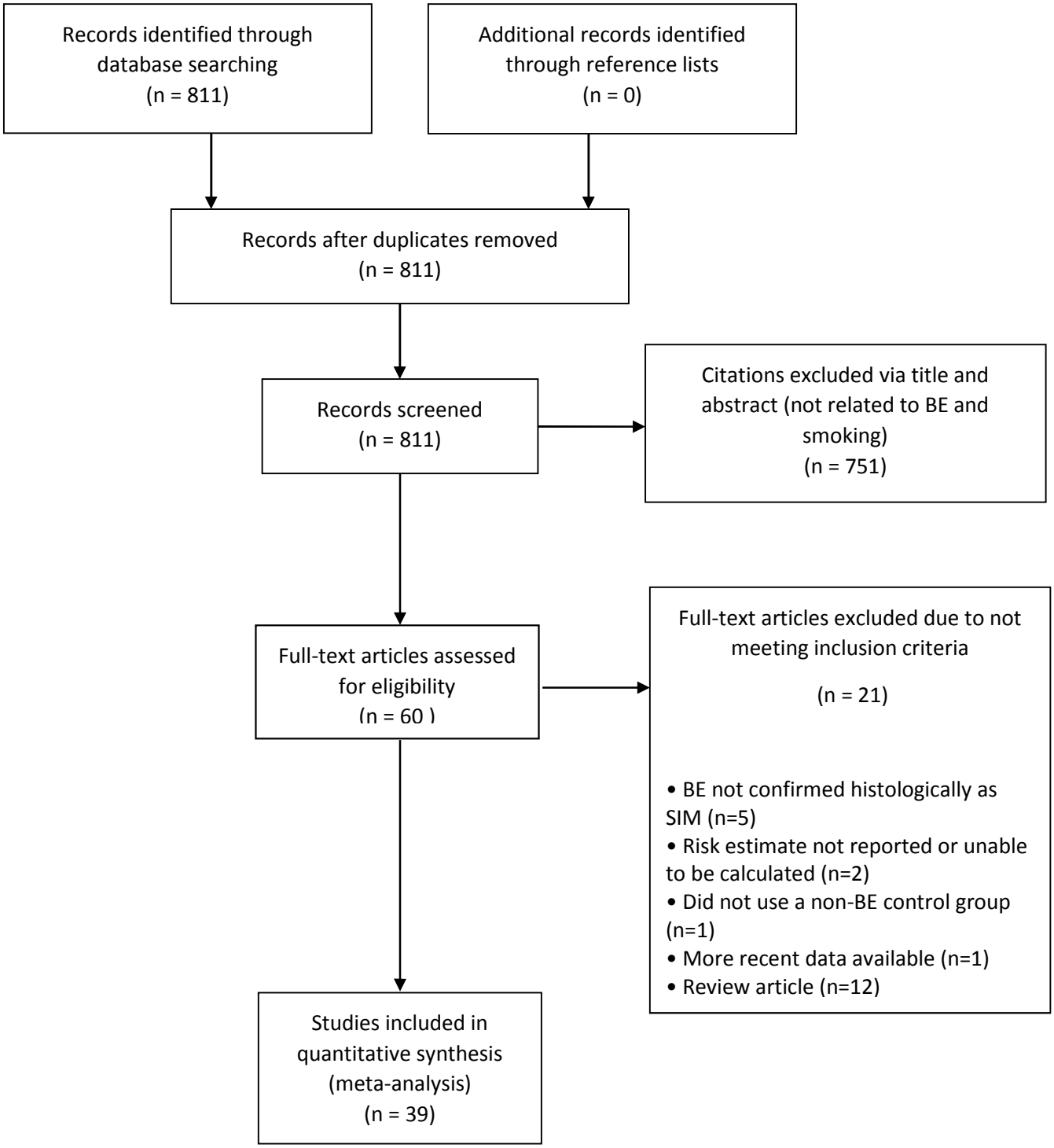
Abbreviations: BE, Barrett’s esophagus; CI, confidence interval; GERD, gastroesophageal reflux disease; LSBE, long segment Barrett's esophagus; OR, odds ratio; SSBE, short segment Barrett's esophagus.

Table 3: Meta-Analysis by Pack-Years Smoked

Pack-year exposure	Studies, *n*	OR (95% CI)	$P_{difference}$	I^2, %	$P_{heterogeneity}$
Lowest pack-years	10	1.41 (1.22, 1.63)	<0.001	0.00	0.490
Highest pack-years	10	1.53 (1.27, 1.84)	<0.001	26.87	0.197

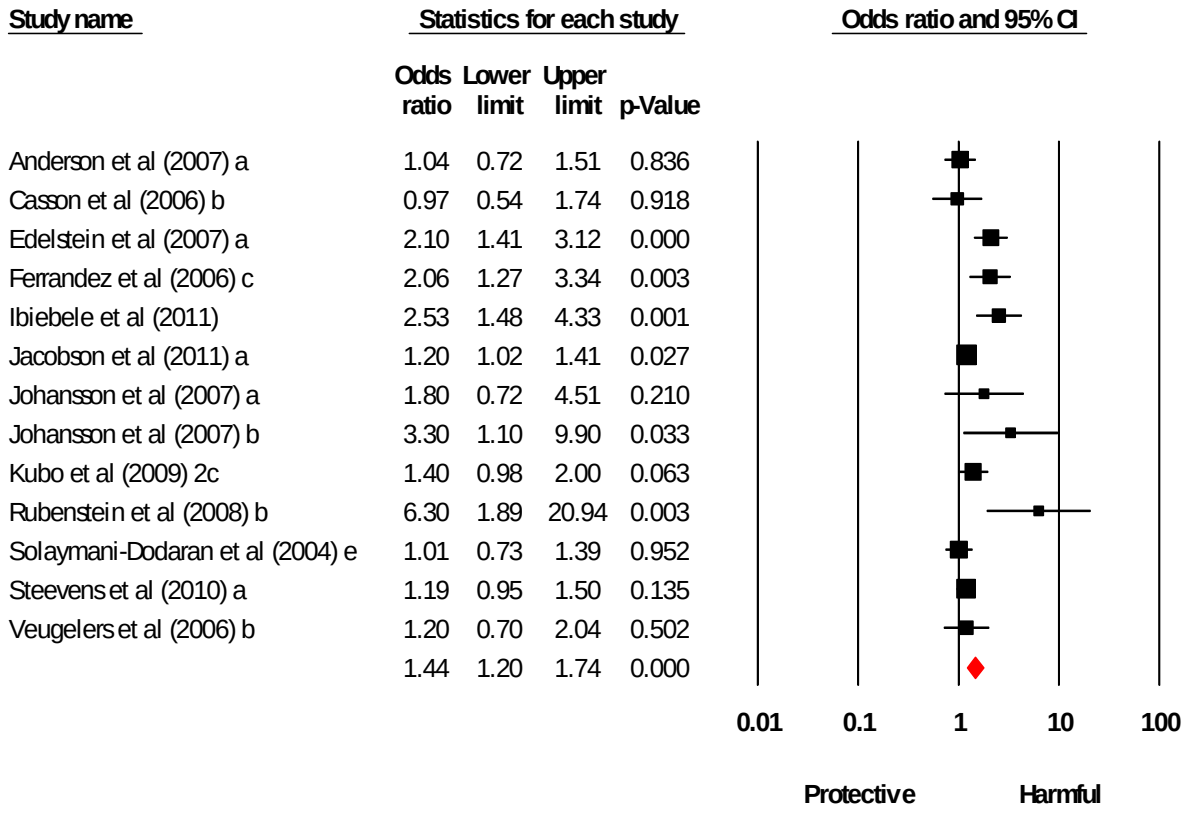
Abbreviations: OR, odds ratio; CI, confidence interval.

Figure 1: Study Selection Flowchart



Abbreviations: BE, Barrett's esophagus; SIM, specialized intestinal metaplasia

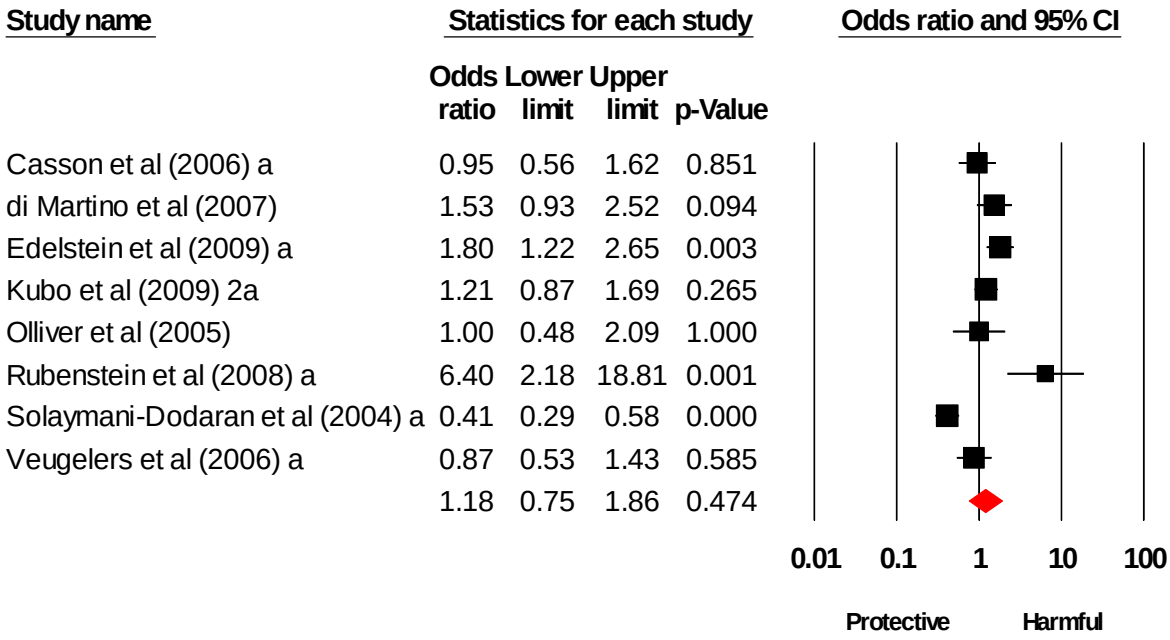
Figure 2: Meta-Analysis of the Association between Ever Smoking and BE, BE Patients versus Non-GERD Controls



Test for heterogeneity I^2=61.73%, p=0.002. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval.

Abbreviations: BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

Figure 3: Meta-Analysis of the Association between Ever Smoking and BE, BE Patients versus GERD Controls



Test for heterogeneity I^2=86.00%, p<0.001. Each study is shown by an odds ratio estimate with the corresponding 95% confidence interval.

Abbreviations: BE, Barrett's esophagus; GERD, gastroesophageal reflux disease.

CHAPTER 4

BARRETT'S ESOPHAGUS AND THE RISK OF COLONIC TUMORS

INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition associated with esophageal adenocarcinoma.[1,2] It involves the replacement of the normal squamous esophageal lining by specialized or intestinal columnar epithelium.[3,4] In North America, BE is diagnosed when endoscopically observed columnar metaplasia is confirmed to contain specialized intestinal epithelia (characterized by the presence of goblet cells) on histological examination.[5]

The possibility of an association between BE and an increased risk of colonic tumors was first raised by Sontaget al.[6] in 1985. This is a clinically significant question because if a relationship is found, it carries implications in terms of screening BE patients for colorectal cancer (CRC). Since then, several studies have reported conflicting results, and the association is not well established. A systematic review in 1995[7] showed a strong association; however, we questioned the authors' methodology, including the use of a synthetic control group constructed by the authors, which appears to have been used in calculating the risk estimates for the studies analyzed. In addition, several new studies have been published since the time of the last systematic review reporting the prevalence of colonic tumors in patients with BE and therefore we considered it appropriate to perform a systematic review that also incorporated these studies.

Our aim was to perform a meta-analysis combining the results of studies reporting the prevalence of colonic tumors in BE vs. controls, and thus provide a quantitative estimate of the risk of colonic tumors associated with BE.

MATERIALS AND METHODS

Study protocol

We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[8] where possible, in performing our systematic review. A systematic search was performed by two reviewers (J.A. and M.T.) through Medline (1950 – present), PubMed (1950 – present), Embase (1947 – present), and Current Contents Connect (1998 – present) through to 7 October 2012, to identify relevant articles. The search used the terms "Barrett's Esophagus" or "Barrett's Esophagus" and "colorectal cancer" or "colon cancer" or "rectal cancer" or "colonic tumors" or "colonic tumors" or "colonic neoplasms", which were searched as text word and as exploded medical subject headings where possible. The reference lists of relevant articles were also searched for appropriate studies. No language restrictions were used in either the search or study selection. A search for unpublished literature was not performed.

Study selection

We included studies that met the following inclusion criteria: (i) the study examined the prevalence of either benign (adenomas) or malignant (CRC) colonic tumors, or both, in BE patients and controls; (ii) the cases were patients diagnosed with BE and the controls were patients without BE; (iii) the risk point estimate was reported as an odds ratio (OR), or the data were presented such that an OR could be calculated; (iv) the 95%confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; (v) an internal comparison was used when calculating the risk estimate. We excluded studies that did not meet the inclusion criteria. Specifically, four studies[9-12] were excluded as they included patients with esophageal adenocarcinoma to

serve as either the cases or controls;three studies[13–15] were excluded as they used an external comparator group and standardized incidence ratios; and one study[16] was excluded as it used an external comparator group made up of groups of patients from previous studies. Studies were included or exclusion following consensus among three authors (J.A., M.T. and G.E.).

Data extraction

We performed the data extraction via a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, temporal direction, population type, country, continent, economic development, case–control matching, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs, and the type of colonic tumor investigated (benign or malignant). Quality of the studies was not assessed and authors were not contacted for missing data. Adjusted ratios were extracted in preference to non-adjusted ratios; however, where ratios were not provided, unadjusted ORs and CIs were calculated. Where more than one adjusted ratio was reported, the ratio with the highest number of adjusted variables was selected. Where multiple risk estimates were available in the same study, for example, studies providing risk estimates for both malignant and benign tumors, they were included as separate risk estimates. Where studies provided only the risk ratio (RR) or hazard ratio (HR), we assumed that the RR or HR would be similar to the OR and thus the RRs and HRs provided were combined with the provided or calculated ORs.

Statistical analysis

We calculated pooled odds ratios and 95% confidence intervals for the effect of BE on the risk of any colonic tumors, as well as on benign colonic tumors and CRC, using a random-effects model.[17] For the relationship between BE and any colonic tumors, we performed subgroup analyses based on studies which adjusted for any variables and specifically for the important confounder of body mass index (BMI), as well as subgroup analyses by temporal study direction (prospective vs. retrospective). We also analyzed the effect of the four[18–21] studies included in our analysis which were in abstract form, and for comparison, also performed an analysis of the three studies[13–15] which were excluded based on their use of an external comparator group.

Heterogeneity was tested with Cochran's Q statistic, with $P < 0.10$ indicating heterogeneity, and quantified the degree of heterogeneity using the I^2 statistic, which represents the percentage of the total variability across studies, which is due to heterogeneity. I^2 values of 25%, 50% and 75% corresponded to low, moderate and high degrees of heterogeneity respectively.[22] Publication bias was quantified using the Egger's regression model.[23] All analyses were performed with Comprehensive Meta-analysis (version 2.0).

RESULTS

Study characteristics

From 1351 studies initially identified, 11[6,18–21,24–29] met our inclusion criteria (Figure 1), of which four[18–21] were abstracts. Selected characteristics of the included studies are presented in Table 1. The studies were all conducted in developed Western countries, with five studies examining European populations, and the remaining six studies

examining North American populations. In terms of study design, one study was a prospective cohort study, and the remainder were retrospective studies. Sample sizes ranged from 96 to 15 093, and BE cases ranged from 32 to 1677. Overall, there were 2580 BE patients and 27 272 participants.

Any colonic tumors

Eleven studies[6,18–21,24–29] comprising of 2580 BE cases, reported an association between colonic tumors (either benign adenomas or CRC) and BE and were included in the analysis. We found an increased risk of colonic tumors in patients with BE, with pooled OR of 1.96 (95% CI, 1.56–2.46) (Figure 2). There was low heterogeneity, which was not statistically significant (I^2 = 15%, P = 0.295). There was no publication bias (P = 0.520), and this was depicted visually on a funnel plot in Figure 3.

We performed sensitivity analyses to assess whether adjustment for confounding variables changed the overall risk estimate. When looking at the five studies[19,24,25,28,29] which adjusted for any variables, the risk of colonic tumors was 1.91 (95% CI, 1.48–2.46), with no heterogeneity (I^2 = 0%, P = 0.591). The six studies[6,18,20,21,27] that did not adjust for any variables showed a risk of colonic tumors of 2.05 (95% CI, 1.29–3.26), with moderate heterogeneity, which was not statistically significant (I^2 = 45%, P = 0.103).

The risk of colonic tumors calculated from the two studies[28,29] which adjusted for BMI was statistically significant (OR 1.89; 95% CI, 1.30–2.76), while that calculated from the

remaining ten studies, which did not adjust for BMI, was 2.02 (95% CI, 1.51–2.70), with moderate heterogeneity, which was not statistically significant (I^2 = 34%, P = 0.161).

When analyzing the ten retrospective studies,[6,18– 21,24–28] the OR was 2.01 (95% CI, 1.58–2.54), with low heterogeneity, which was not statistically significant (I^2 = 17%, P = 0.275). The only prospective cohort study had a risk estimate of 1.23 (95% CI, 0.44-3.43). The pooled risk estimate after removing the four studies[18–21] in abstract form was 1.91 (95% CI, 1.34–2.70). There was moderate heterogeneity, which was not statistically significant (I^2 = 34%, P = 0.161).

The meta-analysis including the three excluded studies[13–15] which used an external comparator group yielded a positive association with an OR of 1.67 (95% CI, 1.35– 2.07), with moderate heterogeneity (I^2 = 50%, P = 0.013). The risk estimate calculated from only the three excluded studies[13–15] was not significant (OR: 1.13, 95% CI, 0.63–2.02). There was a high degree of heterogeneity (I^2 = 84%, P = 0.002).

Benign colonic tumors

Seven studies[6,18,21,24–27] comprising of 361 BE cases and a total of 2568 individuals reported an association between benign colonic tumors and BE and were included in the benign colonic tumors meta-analysis. There was an increased risk of benign colonic tumors in patients with BE, with pooled OR of 1.69 (95% CI, 1.20–2.39) (Figure 4). We found low, statistically insignificant heterogeneity (I^2 = 13%, P = 0.449).

Colorectal Cancer

Six studies[6,19,24,27–29] comprising of 2321 BE cases and 25 793 individuals were included in the meta-analysis for CRC. We found an increased risk of CRC in patients with BE, with pooled OR of 1.90 (95% CI, 1.35–2.67) (Figure 5). There was no heterogeneity (I^2 = 0%, P = 0.452).

DISCUSSION

The meta-analyses showed a statistically significant positive relationship between BE and colonic tumors. This association was stronger for CRC than for benign tumors, although an exact mechanism explaining the association between BE and colonic tumors has not yet been established.

A previous systematic review and meta-analysis by Howden and Hornung[7] found a strong association between BE with specialized columnar epithelium and CRC, with an OR of 8.71. We questioned these authors' use of a 'comparison cohort', which was constructed 'from previously published studies of colorectal cancer screening in the general population'. In addition, the ORs used in the meta-analysis were not the ORs which were published in the original studies, and we were unsure as to how these numbers were obtained. In some instances, the ORs used by Howden and Hornung[7] were larger than the ORs published in the original studies by a factor of four to five. Since their publication, several investigators have disagreed with these large risk estimates.[16,30,31] Our meta-analysis includes four studies [18,25,28,29] which were published subsequent to the Howden and Hornung[7] study and therefore were not included in that study. Although like Howden and Hornung,[7] we also find a statistically significant

association between BE and colonic tumors, there are major issues with the interpretation of our results.

First, only one of the studies included in the analysis, Solaymani-Dodaran et al,[29] was a cohort study which looked at disease incidence over the study period, and it reported a positive but statistically insignificant association (OR: 1.23; 95% CI, 0.44–3.43). A sensitivity analysis excluding the Solaymani-Dodaran et al[29] study yielded a risk estimate of 2.01 (95% CI, 1.58–2.54), with low heterogeneity. The remainder of the studies followed a retrospective study design and therefore were subject to the limitations and biases inherent in studies of that nature. This raises the question as to whether our overall positive result merely reflects biases inherent to retrospective studies, or whether it represents a real association. To ascertain whether a true association between BE and colonic tumors exists, there is a need for more large, prospective studies. The ideal study type would thus be a cohort study that recruited patients with BE and a control group representative of the general population with no colonic tumors at baseline, and observed the incidence of colonic tumors in the two groups over the study period. One problem with such a study would be the ethical issue of performing colonoscopies, which are invasive and carry risks of complications, on young asymptomatic individuals in the absence of any indications. Studies could, however, be carried out in patients aged over 50, in whom colonoscopies are recommended as a screening tool in many countries, including the USA.[32,33] Prospective cohort studies would also be able to establish the existence of a temporal relationship, should one exist, between BE and colonic tumors, which would then have implications for screening.

Our study was also subject to the likely presence of confounders in the individual studies. While we used the adjusted ORs where available, six of the eleven studies did not adjust for confounders, or did not state if such adjustments had been made. This raises the possibility that any observed association could be due to confounders that have not been adjusted for. In the subgroup of four studies that reported adjustments for possible confounders, we still found a significant association between BE and colonic tumors, with no significant change from the unadjusted result. However, of those studies that used adjusted ORs, only two studies adjusted for BMI, which is known to be a risk factor for both BE,[34] and CRC,[35,36] although the strength of the association between BMI and CRC varied with gender and cancer site in both Moghaddam et al[35] and Larsson et al.[36] Additionally, some studies[37,38] found the association of BMI with BE to be insignificant when adjusting for waist-to-hip ratio or waist circumference, which suggests that this association is driven mostly by central adiposity. Our subgroup analysis of the studies that adjusted for BMI (OR: 1.89) vs. those that did not adjust for BMI (OR: 1.80) did not show any appreciable difference. Solaymani-Dodaran et al,[29] the only prospective cohort study in our meta-analysis, did not find a significant association between BE and CRC, but they reported a number of different risk estimates after adjusting for different factors. The risk estimate that included BMI was not significantly different from the risk estimate that excluded BMI, with the BMI adjusted risk at 1.23 (95% CI, 0.44–3.43), and the non-BMI adjusted risk at 1.14 (95% CI, 0.41 3.18), which suggests that in their study, adjustment for BMI did not play a significant role in the risk estimate.

There may also exist a referral or diagnostic bias with respect to BE and colonic tumors. This arises as both are gastrointestinal disorders and may be subject to investigation by

the same physician upon the patient presenting with nonspecific gastrointestinal symptoms and signs such as anemia, which may warrant both upper and lower gastrointestinal endoscopies. One study by Murphy et al,[15] which looked at the risk of CRC associated with BE but was excluded from our analysis because it did not use an internal comparator group, found that the standardized incidence ratio of CRC rose progressively as the follow-up period approached the time of BE diagnosis, thus raising the possibility of diagnostic bias.

Even though we found no statistical heterogeneity in our meta-analyses, studies with differing designs and methodologies were included in the analysis. Specifically, we looked at one cohort study and ten retrospective studies, with four of the studies being in the form of abstracts. There existed also differences in the control groups between studies. Some of the patients were asymptomatic, while others were being investigated for gastrointestinal symptoms related to irritable bowel syndrome and even rectal bleeding. This may impact the risk estimates and add to the diagnostic bias discussed above, as well as contribute to heterogeneity.

Additionally, our meta-analysis only comprised eleven studies, with the subgroup analyses of CRC and benign adenomas comprising six and seven studies respectively. All but one of the studies were retrospective in nature. Adjusted ORs were only available in five studies, and of those, only two adjusted for the confounder of BMI. For comparison, we performed an analysis based on the three studies[13–15] which used an external comparator group. The studies reported conflicting results, with de Jonge et al[14] reporting a positive, statistically significant association, and neither Murphy et al.15nor Cook et al[13] finding an association. The overall pooled risk estimate was

positive, but not statistically significant. This analysis is only based on only three studies which reported conflicting results, so while it is difficult to make a meaningful definitive comment on the impact their exclusion had on our results, it does not appear to have greatly influenced our result. The analysis with these studies included yielded a risk estimate of 1.67, which, while lower than the risk estimate of 1.96 obtained with the studies excluded, is still positive and still statistically significant.

Our analysis included four studies which were published in abstract form, and to see if these had a significant impact on our overall results, we performed a subgroup analysis excluding the abstracts. No appreciable difference was found when removing these studies from the pooled risk estimate for any colonic tumors (OR: 1.91 with the abstracts removed vs. OR: 1.96), with the results maintaining statistical significance. This suggests that the abstracts did not have a large impact on the overall results.

Notwithstanding the current lack of an established mechanism to explain the relationship between BE and colonic tumors, the existence of a positive association between the two as ascertained by our meta-analysis warrants a call for more large cohort studies to elucidate whether the relationship is a real one and not a result of bias. Should the association then be shown to be real, this discovery would carry a number of important implications. First, an established association will warrant a search for common genetic or environmental risk factors as well as more studies in basic science to establish a mechanism for and thus provide a better understanding of the association. Secondly, it will raise the important clinical question as to whether BE patients should be regularly screened for CRC, which several investigators[19, 24, 25] have considered unwarranted due to inconclusive data, a view which we agree with at

present. The CRC risk estimate in our study, 1.88 (95% CI, 1.32–2.68), is comparable to the increased risk of CRC in first degree relatives of patients with CRC of 2.24 (95% CI, 2.06–2.43), as reported in a recent meta-analysis by Butterworth et al.[39] Most of the studies included in that meta-analysis reported risk estimates between 1.5 and 4, which again is comparable to the association we found between BE and CRC. In addition, a more recent Italian study Castiglione et al,[40] found the risk of CRC in first degree relatives of CRC patients to be 1.53 (95% CI, 1.27–1.83), also comparable to our risk estimate. If the risk estimates for CRC in patients with BE reflects a real relationship, this risk for CRC is similar to that found in first degree relatives of patients with CRC, and serious consideration may need to be given in the future to screening BE patients for CRC.

Our study had a number of strengths. The MOOSE guidelines were followed where possible. We performed a thorough search through four databases with no language restrictions. Studies using external comparators were excluded. The use of an internal control group is recognized as superior in terms of study design,[41–43] and by excluding studies that used external comparators, we added statistical rigor to our analysis. Additionally, we observed no statistically significant heterogeneity in any of our analyses, and publication bias was not present.

In summary, our results suggest that BE is associated with an increased risk of colonic tumors. The association was present for both benign and CRC, but was stronger for CRC. More prospective cohort studies adjusting for possible confounders are needed to further elucidate this relationship. At present, we recommend against screening BE

patients for CRC due to the lack of robust prospective evidence supporting this association.

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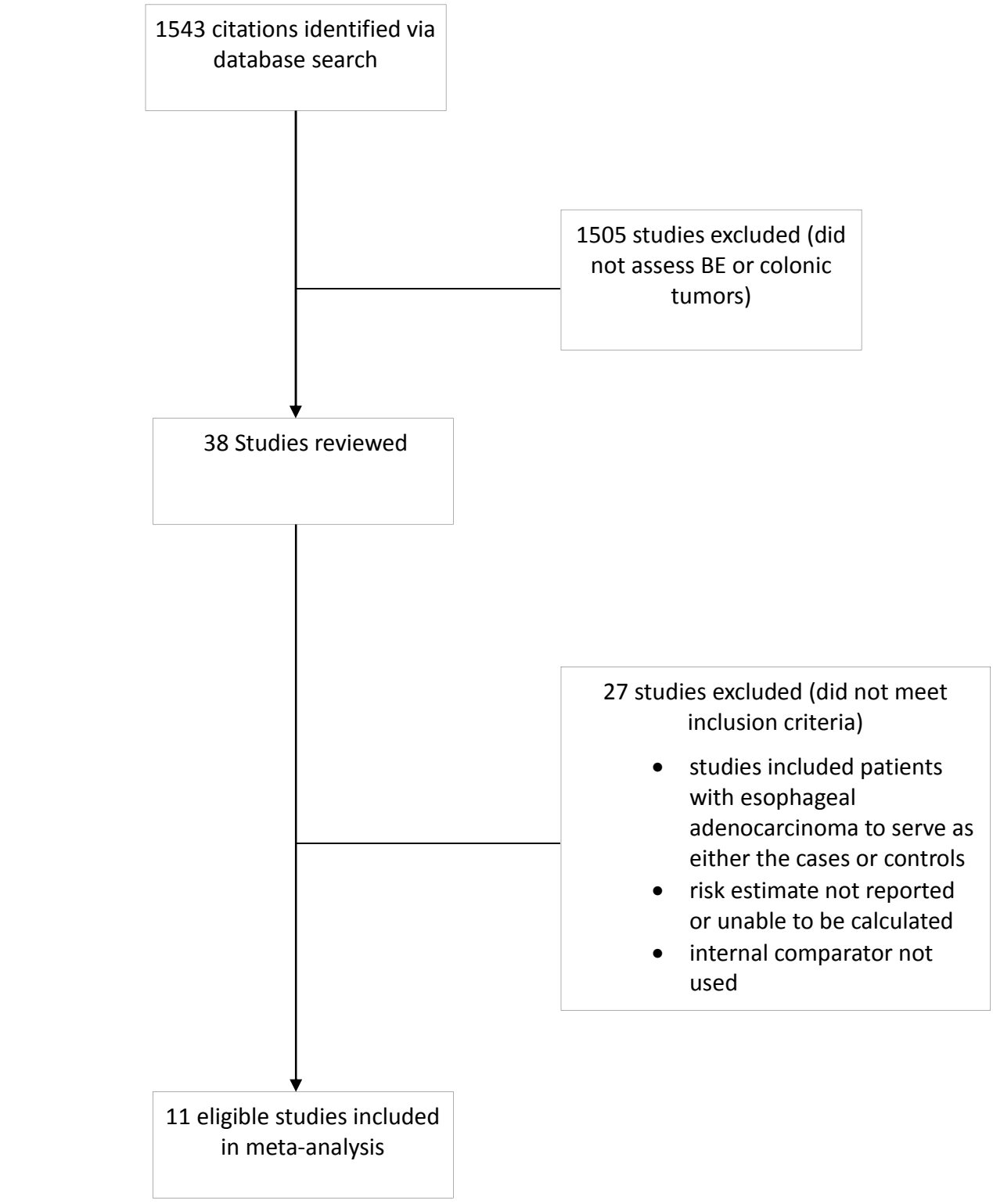
Table 1: Studies reporting prevalence of any colonic tumors in BE patients which were included in the Meta-analysis

Authors	Year	Temporal Direction (prospective or retrospective	Country	Cases	Controls	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Colonic tumor investigated
Cauvin *et al.*[24] a	1995	Retrospective	France	BE patients	Consecutive patients with symptoms suggestive of IBS	Age, gender, family history of CRC, rectal bleeding	None	104	641	Benign (adenomas)
Cauvin *et al.*[24] b	1995	Retrospective	France	BE patients	Consecutive patients with symptoms suggestive of IBS	Age, gender, family history of CRC, rectal bleeding	None	104	641	Malignant
Elli *et al.*[18]	2010	Retrospective	Italy	BE patients	Patients who underwent esophagogastroduodenoscopyand colonoscopy.	Not stated	NA	NA	1018	Benign (colon polyps
Gerson *et al.*[25]	2002	Retrospective	USA	BE patients free from GERD symptoms, who were undergoing sigmoidoscopy for CRC screening	Patients free from GERD symptoms, who were undergoing sigmoidoscopy for CRC screening	Age	None	44	110	Benign (colon polyps)
Laitakari *et al.*[26]	1995	Retrospective	Finland	BE patients	Patients referred to hospital for benign thyroid, inguinal hernia or hand surgery, who had been attending urological or vascular examinations	None	None	72	99	Benign (adenomas)
Limburg *et al.*[19]	1994	Retrospective	USA	BE patients	Patients with peptic ulcer disease and gastric polyps	Age, gender, time between first colonoscopy and esophagogastro-duodenoscopy		175	8922	Malignant (CRC at any site)
Lyons *et al.*[20]	1993	Retrospective	USA	BE patients	Patients with gastroesophageal reflux with stricture	None	None	99	153	Both benign and malignant
Robertson *et al.*[27] a	1989	Retrospective	UK	BE patients	Patients clinically diagnosed IBS	None	Age and gender	32	96	Benign (polyps and adenomas)

Authors	Year	Temporal Direction (prospective or retrospective	Country	Cases	Controls	Adjusted Variables	Case-control matching	Number of Cases	Total Size	Colonic tumor investigated
Robertson *et al.*[27] b	1989	Retrospective	UK	BE patients	Patients clinically diagnosed IBS	None	Age and gender	32	96	Malignant
Robertson *et al.*[27] c	1989	Retrospective	UK	BE patients	Patients clinically diagnosed IBS	None	Age and gender	32	96	Both benign (polyps and adenomas) and malignant
Rothstein *et al.*[21]	1991	Retrospective	USA	BE patients	Patients undergoing upper and lower endoscopic surveillance in the workup of an iron deficiency anemia	None	None	44	99	Benign polyps
Siersema *et al.*[28] a	2006	Retrospective	USA	BE patients	Patients who had had undergone upper GI endoscopy within 14 days of the corresponding case	Age, BMI, other malignancies, use of PPIs, use of aspirin/NSAIDS, alcohol consumption, smoking status	Date of endoscopy	268	536	Both benign and malignant
Siersema *et al.*[28] b	2006	Retrospective	USA	BE patients	Patients who had had undergone upper GI endoscopy within 14 days of the corresponding case	Age, BMI, other malignancies, use of PPIs, use of aspirin/NSAIDS, alcohol consumption, smoking status	Date of endoscopy	268	536	Malignant
Solaymani-Dodaran*et al.*[29]	2004	Prospective	UK	BE patients	Patients on the GP database with no restriction other than not having BE	Age, gender, number of visits per year, smoking, alcohol and BMI	Age, gender and GP practice	1677	15 093	Malignant
Sontag *et al.*[6] a	1985	Retrospective	USA	BE patients	Patients who underwent colonoscopy for occult blood in stool, weight loss, rectal bleeding, or abdominal pain	None	None	65	505	Benign
Sontag *et al.*[6] b	1985	Retrospective	USA	BE patients	Patients who underwent colonoscopy for occult blood in stool, weight loss, rectal bleeding, or abdominal pain	None	None	65	505	Malignant
Sontag *et al.*[6] c	1985	Retrospective	USA	BE patients	Patients who underwent colonoscopy for occult blood in stool, weight loss, rectal bleeding, or abdominal pain	None	None	65	505	Both benign and malignant

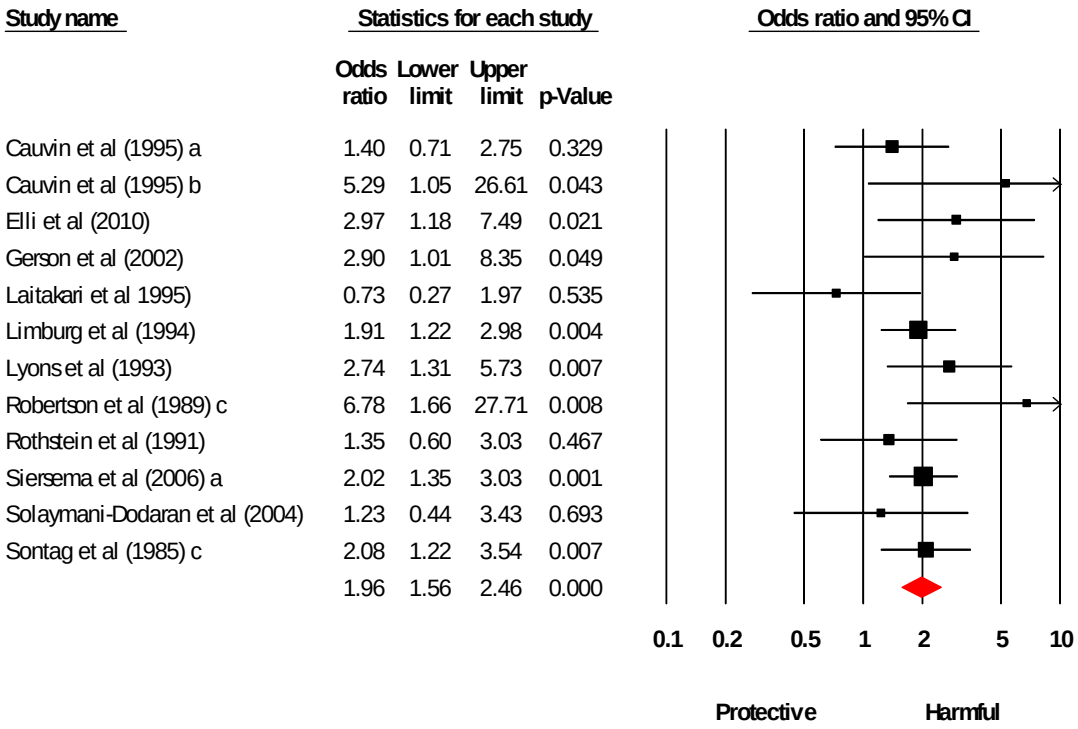
Abbreviations: BE, Barrett's esophagus; IBS, irritable bowel syndrome; CRC, colorectal cancer; GERD, gastroesophageal reflux disease; GI, gastrointestinal; BMI, body mass index; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory; GP, general practitioner; NA, not available.

Figure 1: Study Selection Flowchart



Abbreviations: BE, Barrett's esophagus

Figure 2: Meta-Analysis of BE and any colonic tumours



Abbreviations: BE, Barrett's esophagus

Figure 3: Funnel plot to assess publication bias

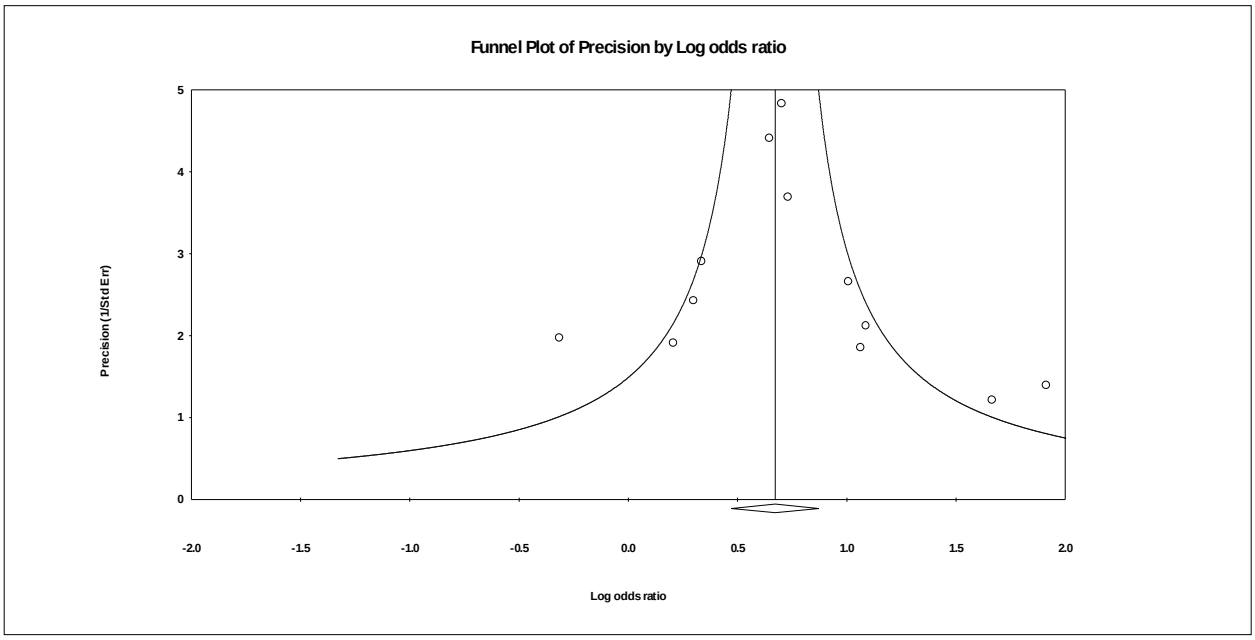
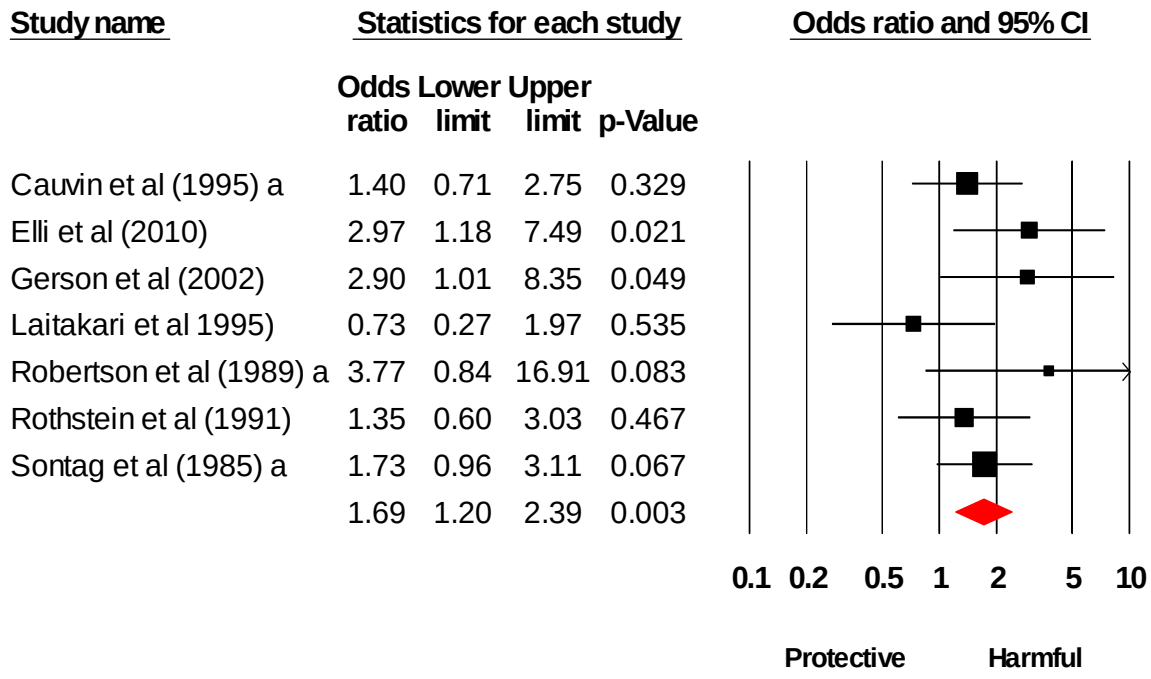
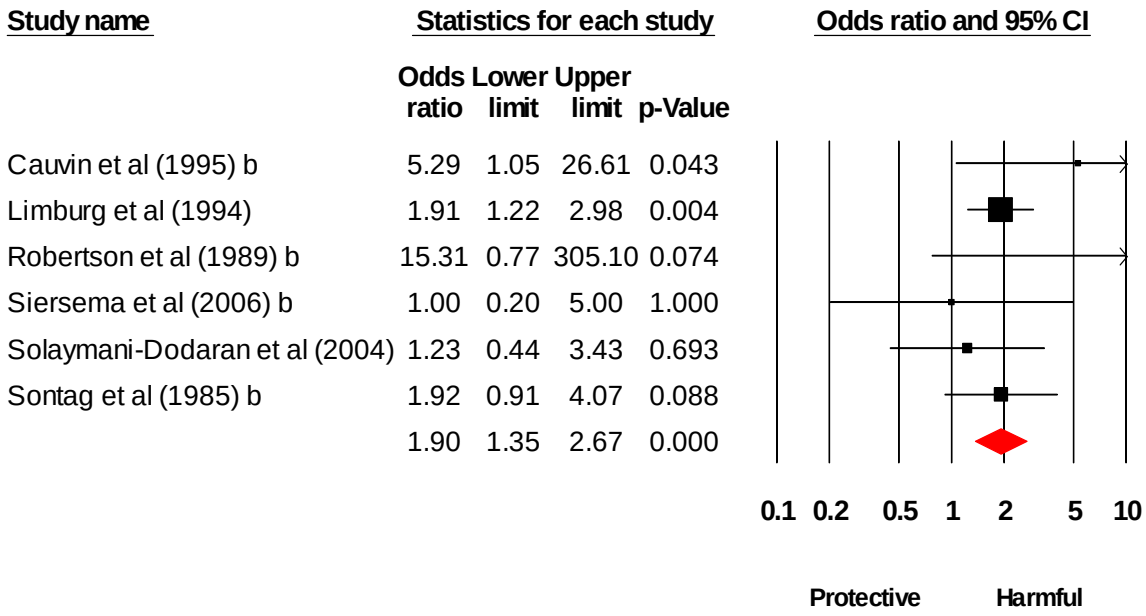


Figure 4: Meta-Analysis of BE and benign colonic tumors



Abbreviations: BE, Barrett's esophagus

Figure 5: Meta-Analysis of BE and malignant colonic tumors



Abbreviations: BE, Barrett's esophagus

CHAPTER 5

SUMMARY AND CONCLUSIONS

The purpose of the work contained within this thesis was to further expand on the knowledge of the epidemiology of Barrett's esophagus (BE). In particular, Chapters 2-4 contain meta-analyses which examine and quantify the association between BE and hiatal hernia, cigarette smoking, and colonic tumors, respectively.

Hiatal hernia has a long and clinically well-established relationship with BE, however the relationship has not yet been quantified through a meta-analysis. In conducting a meta-analysis on the topic, I have for the first time quantified the association and also found the relationship to be stronger for long segment BE than for short segment BE. Furthermore, it is usually assumed that the relationship between hiatal hernia and BE is due to hiatal hernia predisposing to reflux, which then damages the esophageal epithelium, resulting in BE.[1,2] As part of our study, a subgroup analysis was performed by studies which adjusted for reflux. This showed that the relationship between hiatal hernia and BE remained even after adjusting for reflux, with an odds ration of 3.35 (95% CI, 2.25–4.39) for the association between hiatal hernia and any length of BE and 13.84 (95% CI, 5.19–36.89) for long segment BE. This finding of an association between hiatal hernia and BE independent of reflux is an important one and supports the hypothesis that the relationship is a real one, rather than a result of confounding factors.

Environmental factors such as smoking, although well established as risk factors for squamous cell carcinoma of the esophagus,[3] have to date not been definitively implicated in the development of BE or adenocarcinoma. Although a recent pooled analysis of 5 case control studies from the International Barrett's and Esophageal Adenocarcinoma Consortium ("BEACON")[4] finding a positive relationship between cigarette smoking and BE has been published, ours was the first meta-analysis of the relationship and included, in addition to the BEACON studies, a large number of other studies. Confirming the findings in the BEACON pooled analysis, we found a positive association between smoking and BE. Although we did not observe a convincing dose response - the odds ratios for the

lowest pack-year and highest pack-year groups were 1.41 and 1.53, respectively, with overlapping confidence intervals - the positive association was observed across subgroup analyses. Furthermore, the relationship was stronger when adjusting for confounders such as obesity, age and gender. Our study was the largest to date on the topic and represents arguably the strongest evidence of a link between cigarette smoking and BE. It is also an exciting finding, because if the relationship is real, smoking represents one of the few known modifiable risk factors for BE, and this could therefore be important in counseling patients on reducing the risk of developing BE.

An intriguing possibility is the association between BE and tumors of the colon, both benign and malignant. Although first raised in 1985,[5] the issue remains unresolved despite a number of studies and an earlier meta-analysis[6] published on the subject since then. Ours is the second meta-analysis studying the association and incorporates more recent studies published since the last meta-analysis was performed in 1995. We found a positive and statistically significant relationship between BE and colonic tumors. This relationship remained in the subgroup analyses which adjusted for confounding factors and specifically for body mass index, although only two studies constituted the latter group. The association was present for both benign and colorectal cancer (CRC), but was stronger for CRC. This potential association is significant clinically because if patients with BE are at increased risk of CRC, it raises the question of whether they should be screened earlier for CRC than is recommended for the general population. Despite our positive results, at present, we recommend against screening BE patients for CRC due to the lack of robust prospective evidence supporting this association. However, it will be interesting to observe the results of future prospective cohort studies adjusting for possible confounders.

In summary, the three meta-analyses incorporated in this thesis examined and quantified, respectively, the association between BE and hiatal hernia, cigarette smoking, and colonic tumors.

The results showed positive associations for the relationships studied. It is hoped that this work will contribute towards the existing body of knowledge on BE and its risk factors and associations.

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