Meta-Analysis

The Incidence of Esophageal Cancer and High-Grade Dysplasia in Barrett's Esophagus: A Systematic Review and Meta-Analysis

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Barrett's esophagus is a well-recognized precursor of esophageal adenocarcinoma. Surveillance of Barrett's esophagus patients is recommended to detect high-grade dysplasia (HGD) or early cancer. Because of wide variation in the published cancer incidence in Barrett's esophagus, the authors undertook a systematic review and meta-analysis of cancer and HGD incidence in Barrett's esophagus. Ovid Medline (Ovid Technologies, Inc., New York, New York) and EMBASE (Elsevier, Amsterdam, the Netherlands) databases were searched for papers published between 1950 and 2006 that reported the cancer/HGD risk in Barrett's esophagus. Where possible, early incident cancers/HGD were excluded, as were patients with HGD at baseline. Forty-seven studies were included in the main analysis, and the pooled estimate for cancer incidence in Barrett's esophagus was 6.1/1,000 person-years, 5.3/1,000 person-years when early incident cancers were excluded, and 4.1/1,000 person-years when both early incident cancer and HGD at baseline were excluded. Corresponding figures for combined HGD/cancer incidence were 10.0 person-years, 9.3 person-years, and 9.1/1,000 person-years. Compared with women, men progressed to cancer at twice the rate. Cancer or HGD/cancer incidences were lower when only high-quality studies were analyzed (3.9/1,000 person-years and 7.7/1,000 person-years, respectively). The pooled estimates of cancer and HGD incidence were low, suggesting that the cost-effectiveness of surveillance is questionable unless it can be targeted to those with the highest cancer risk.

adenocarcinoma; Barrett esophagus; esophageal neoplasms; incidence; meta-analysis; review

Abbreviations: CI, confidence interval; LSBE, long-segment Barrett's esophagus; SIM, specialized intestinal metaplasia; SSBE, short-segment Barrett's esophagus.

In recent decades, the incidence of esophageal adenocarcinoma in the United States and Western Europe has risen at a more rapid rate than that of any other malignant neoplasm (1–5). It is now the most common type of esophageal cancer in these countries (6)

Barrett's esophagus is well recognized as a precursor of the majority of cases of esophageal adenocarcinoma (7). It has been estimated that Barrett's esophagus carries a risk of cancer 30–125 times greater than that for an age-matched population (8). Five-year survival following a diagnosis of esophageal adenocarcinoma is less than 15 percent (9, 10). Hence, Barrett's esophagus surveillance has been recommended to detect dysplasia and early carcinoma (11, 12). Several studies have now shown that patients diagnosed with esophageal adenocarcinoma within a surveillance program have earlier-stage disease and longer survival times than patients diagnosed outside such programs (13–15). However, the cost-effectiveness of Barrett's esophagus

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surveillance is dependent on cancer risk (16). Wide variation in this risk has been observed, ranging from 0 percent to 3 percent per annum (17).

To date, there have been three known published systematic reviews of the incidence of cancer in Barrett's esophagus (17–19). However, in all three, the literature search was limited to studies published in the English language, and two searched only the Medline database (17, 18). In addition, one of these included only those patients who had undergone medical or surgical treatment (18), and two of the studies (17, 18) did not include high-grade dysplasia as an outcome. Furthermore, patients with high-grade dysplasia at baseline, who have a high risk of progression to malignancy (20–25), were not excluded from any of the studies, and quality criteria for the selection of studies were not applied.

We undertook this systematic review to include all papers irrespective of language of publication and to exclude prevalent high-grade dysplasia. We included high-grade dysplasia as an outcome, applied quality criteria to the studies, and undertook analyses based on them. We also investigated the variation in cancer/high-grade dysplasia incidence in Barrett's esophagus by geographic location and other factors such as length of Barrett's segment and sex.

MATERIALS AND METHODS

Both Ovid Medline (Ovid Technologies, Inc., New York, New York) and EMBASE (Elsevier, Amsterdam, the Netherlands) databases were searched for all papers published in any language between 1950 and 2006 that reported the cancer or high-grade dysplasia risk in Barrett's esophagus. The two main search strategies combined the results of keyword searches for Barrett's esophagus and for cancer. The following keywords for Barrett's esophagus were used: Barrett's esophagus, Barrett's metaplasia, Barrett's mucosa, Barrett's epithelium, columnar lined esophagus, or specialized intestinal metaplasia (SIM). The keywords used for cancer and dysplasia were the following: adenocarcinoma, esophageal cancer, esophageal neoplasm, esophageal neoplasia, adenosquamous tumor, or dysplasia. These terms were used as keyword and mapped terms, and both American and English spellings were allowed.

Duplicate publications were removed. Each title and abstract was independently reviewed by two researchers to determine whether the paper was relevant to the review topic. The full text was reviewed if the abstract indicated that the paper reported cancer or high-grade dysplasia risk in Barrett's esophagus patients. The bibliographies of these articles were also scanned to identify additional articles. Papers were incorporated in the review if they included a follow-up period and reported the incidence of esophageal cancer or high-grade dysplasia in Barrett's esophagus irrespective of the definition of Barrett's esophagus used—for example, endoscopically or histologically confirmed, short-segment Barrett's esophagus (SSBE) or long-segment Barrett's esophagus (LSBE), SIM present or not.

Studies were excluded if

- they were available as abstracts only.
- they reported esophageal cancer incidence in familial Barrett's esophagus patients.
- they reported esophageal cancer incidence in Barrett's esophagus in intellectually disabled patients.
- they reported esophageal cancer incidence in Barrett's esophagus in children.
- they reported only those patients who underwent antireflux surgery.
- all patients had dysplasia at baseline.

If serial publications reported cancer risk in the same cohort, only the most recent report was included. However, information was obtained from earlier reports for subgroup analysis if the most recent studies did not include the required information.

Data extraction

The first author (F. Y.) and one of the other authors (L. M., M. C., or K. G.) extracted data independently from each study by using standardized proformas (this data extraction form is posted on the *Journal*'s website (http://aje.oupjournals. org/)), and any disagreement was resolved by discussion. The following data were extracted, where available: study location; year and language of publication; definition of Barrett's esophagus used; number of patients in the study; number of patients for whom follow-up information was available; mean follow-up period; person-years of follow-up; mean age of patients; and proportion of patients at baseline who were male, were female, had LSBE (≥3 cm) or SSBE (<3 cm), had SIM, or had low-grade dysplasia or high-grade dysplasia. The following data were also collected, where available, to evaluate the outcomes of interest: total number of cancers and high-grade dysplasias, number of incident cancers and high-grade dysplasias (if patients developed a cancer after high-grade dysplasia, only the cancer was counted), period used to exclude early incident cancer and high-grade dysplasias, and number of early incident cancers and high-grade dysplasias. When the authors of the reports excluded early incident cancers, it generally was for those occurring within the first 6 or 12 months after Barrett's esophagus diagnosis. Both thresholds were accepted unless cancers occurring between 6 and 12 months could be excluded on further examination of the published data. In general, the authors of the reports did not exclude high-grade dysplasias occurring within the first year, but some reports provided information to enable these cases to be excluded.

Quality criteria

Three factors were considered indicators of good study quality: 1) large study size (i.e., ≥500 person-years), 2) application of a robust definition of Barrett's esophagus—clinically visible segment and histologically confirmed SIM, and 3) low likelihood of selection bias. Selection bias was assessed by calculating the proportion of all Barrett's esophagus patients in the population under study for whom follow-up data were provided (or for whom follow-up was not appropriate, e.g., prevalent esophageal cancer). Studies that did not provide information to enable this proportion to be calculated or in which the proportion was less than

70 percent were considered to be affected by selection bias. Exclusion of studies on the basis of each of these quality criteria would have resulted in the omission of 23, 32, and 18 studies, respectively. If all quality criteria had been applied, all but eight studies would have been excluded. Therefore, instead of excluding these studies, we conducted subgroup analyses according to the criteria.

Calculating esophageal cancer and high-grade dysplasia incidence in each study

All studies excluded prevalent cancers at baseline. For each study, the incidence of cancer in Barrett's esophagus was calculated by dividing the number of incident cancers by the total number of person-years of observation. When the information could be extracted, participants with early incident cancer (cancer occurring in the first year) and high-grade dysplasia at baseline were excluded. If the total number of person-years of follow-up was not reported, it was calculated by multiplying the number of patients under follow-up by mean duration of follow-up. For studies that reported median age only, this information was used to approximate mean age. The combined incidence of cancer and high-grade dysplasia was calculated in a similar way.

Pooled analyses

Exact methods, based on the Poisson distribution, were used to calculate 95 percent confidence intervals for the rate of cancer/high-grade dysplasia for presentation in forest plots. Meta-analysis models were applied by using the log incidence rates of cancer/high-grade dysplasia and corresponding standard errors. When the counts of cancer/high-grade dysplasia were zero, a correction of 0.5 was added to the number of cases and person-years of follow-up, prior to calculation, as previously described (26). Heterogeneity between studies was investigated by using the χ^2 test and was measured by using the I^2 statistic (27). The I^2 statistic measures the proportion of variation in the study estimates due to heterogeneity. A random-effects model (28) was used to calculate a pooled estimate of the incidence rate from the combined studies.

An alternative analysis that did not involve any corrections for zero counts of cancer/high-grade dysplasia was conducted by using a two-stage method (29) to summarize the incidence rate at the study level and to produce an average incidence rate (and 95 percent confidence interval) based upon the mean and standard deviation of the study incidence rates. This analysis produced similar results and is therefore not shown in this paper.

Publication bias was investigated by examining funnel plots and by using Begg's and Egger's test that used a liner regression approach to measure funnel plot asymmetry on the natural logarithm scale of odds ratio (30, 31). All statistical analyses were performed by using Stata version 9.2 software (Stata Corporation, College Station, Texas).

All studies that met inclusion criteria were included in the principal analyses. Repeat analyses included only those studies in which early incident cancers or patients with high-grade dysplasia at baseline could be excluded. Sub-

group analyses, which were identified a priori, were performed on the basis of the quality criteria and according to sex, length of segment, presence of SIM, and definition of Barrett's esophagus used.

RESULTS

The Ovid Medline and EMBASE searches yielded 3,896 and 5,610 entries, respectively (figure 1). Following removal of duplicates, 7,780 abstracts were assessed and 209 articles appeared to be appropriate for inclusion in the review. The full-text papers were evaluated, and 80 papers met the criteria. Another nine papers were added following review of the bibliographies of these papers. Data were extracted from these 89 studies. Nineteen studies (32–50) were excluded because the incidence of cancer or high-grade dysplasia in Barrett's esophagus could not be calculated, and 23 repeated studies (51–73) were also excluded. Forty-seven studies (74–120) were therefore included in the analysis of cancer incidence in Barrett's esophagus patients (figure 1).

Study characteristics

Of the 47 studies included in the review, 17 were from the United Kingdom, 13 from other European countries, 13 from the United States, and four from other countries. The overall mean age was 59.6 years in the 35 studies providing this information. Twenty-seven studies reported the sex of the Barrett's esophagus patients, with a mean overall male percentage of 68 percent. Twenty-five studies reported the length of Barrett's esophagus, and the mean percentage of LSBE was 92 and the mean percentage of SSBE was 7.7 in these studies. Twenty-five studies reported the percentage of Barrett's esophagus patients with SIM, and the overall mean percentage who were SIM positive was 90 percent. Seventeen studies reported the proportion of Barrett's esophagus patients undergoing routine surveillance, with an overall mean of 77 percent. Twenty-one studies reported the percentage of Barrett's esophagus with low-grade dysplasia at baseline: the overall percentage of low-grade dysplasia in these studies was 15.7 percent (table 1).

Overall incidence of cancer in Barrett's esophagus. All 47 studies provided data that could be used for the analysis of cancer incidence in Barrett's esophagus patients. The studies included 11,279 patients followed up for 47,496 person-years, in whom 209 cancers occurred. The average cancer incidence in Barrett's esophagus was 6.1 per 1,000 person-years (95 percent confidence interval (CI): 4.7, 7.9) (figure 2). However, there was evidence of considerable heterogeneity in the incidence rates ($\chi^2 = 135.4$, df = 46, $p < 0.001$; $I^2 = 66$ percent). In 29 studies in which the early incident cancers within 1 year could be excluded, the average incidence rate of cancer in Barrett's esophagus was 5.3 per 1,000 person-years (95 percent CI: 3.8, 7.4), but again there was marked heterogeneity ($\chi^2 = 77.4$, df = 28, $p < 001$; $I^2 = 64$ percent). In 12 studies, both the early incident cancers and patients with high-grade dysplasia at baseline could be removed, the average incidence rate was 4.1 per 1,000 person-years (95 percent CI: 3.1, 5.5), and there was
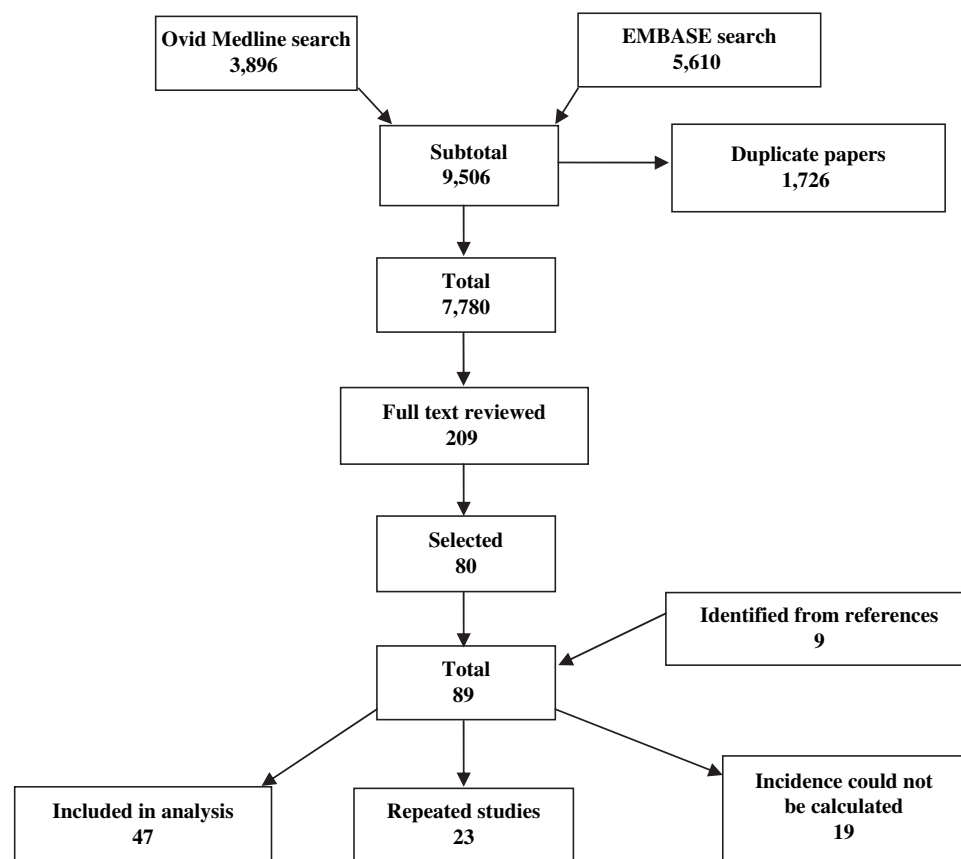
FIGURE 1. Search strategy used and number of studies included at each stage of the meta-analysis. Ovid Medline: Ovid Technologies, Inc., New York, New York; EMBASE (The Excerpta Medica Database): Elsevier, Amsterdam, the Netherlands).

little evidence of heterogeneity ($\chi^2 = 9.4$, df $= 11$, $p = 0.58$; $I^2 = 0$).

The mean incidence rate in the United Kingdom studies was 7.0 per 1,000 person-years (95 percent CI: 4.2, 11.5). In US studies, it was 6.4 per 1,000 person-years (95 percent CI: 4.1, 9.8), and in other European countries studies it was 5.6 per 1,000 person-years (95 percent CI: 3.7, 8.5).

Incidence of both cancer and high-grade dysplasia. Twenty-five studies (45, 62, 68, 74, 79, 80, 85–87, 90, 91, 94–100, 109, 111–115, 119) provided data on the incidence of high-grade dysplasia as well as cancer. These studies included 4,491 patients followed up for 22,609 person-years, with 99 incident cancers and 79 incident cases of high-grade dysplasia. There was evidence of marked heterogeneity in this pooled analysis ($\chi^2 = 106.7$, df $= 24$, $p < 0.001$; $I^2 = 77$ percent). The pooled incidence of cancer or high-grade dysplasia was 10.0 per 1,000 person-years (95 percent CI: 7.1, 14.2) (figure 3). In 18 studies, it was possible to exclude both early incident cancer and high-grade dysplasia within the first year of follow-up and the pooled estimate was 9.3 per 1,000 person-years (95 percent CI: 6.3, 14), but heterogeneity remained ($\chi^2 = 84.8$, df $= 17$, $p < 0.001$; $I^2 = 80$ percent). In 10 studies in which it was pos-

sible to exclude high-grade dysplasia at baseline, the pooled estimate of cancer or high-grade dysplasia was 9.1 per 1,000 person-years (95 percent CI: 5.9, 13.8), but again there was marked heterogeneity ($\chi^2 = 29.2$, df $= 9$, $p = 0.0006$; $I^2 = 69$ percent).

Subgroup analysis

Table 2 shows the results of subgroup analyses. Six studies (61, 66, 84, 89, 98, 108) reported the incidence of cancer in men, giving a pooled estimate of 10.2 per 1,000 person-years. The pooled incidence in females (five studies (61, 84, 89, 98, 108)) was 4.5 per 1,000 person-years. Twenty-six studies (52, 54, 60, 66, 67, 73, 75, 76, 81, 83, 85, 88, 89, 92, 93, 96, 97, 101, 102, 105, 107, 111, 116–118, 120) reported the incidence of cancer in LSBE, with a pooled estimate of 6.7 per 1,000 person-years, while the pooled incidence in SSBE (six studies (54, 63, 64, 74, 86, 102)) was 6.1 per 1,000 person-years. Twenty studies (45, 74, 77, 80, 85, 86, 91, 94, 96–98, 102, 103, 109, 112–115, 118, 119) reported the incidence of cancer in SIM, producing a pooled estimate of 4.7 per 1,000 person-years.

TABLE 1.   Studies included in the systematic review and meta-analysis of the incidence of cancer in Barrett's esophagus

First author (reference no.)	Country	Year	Language	No. of patients under follow-up	Mean age (years)	Male (%)	Female (%)	LSBE* (%)	SSBE* (%)	SIM* (%)	LGD* (%)
Spechler (82)	United States	1984	English	105	NA*	NA	NA	NA	NA	100.0	NA
Cameron (92)	United States	1985	English	104	59.6	67.3	32.7	100.0	0.0	NA	NA
Cooper (93)	New Zealand	1987	English	33	NA	NA	NA	100.0	0.0	NA	0.0
Garcia Marcilla (117)	Spain	1989	Spanish	130	50.6	NA	NA	100.0	0.0	NA	NA
Ovaska (81)	United Kingdom	1989	English	26	NA	NA	NA	100.0	0.0	NA	NA
Skinner† (110)	United States	1989	English	45	NA	NA	NA	NA	NA	NA	NA
Miros† (111)	Australia	1991	English	107	63.3	NA	NA	100.0	0.0	NA	9.4
Watson (105)	United Kingdom	1991	English	45	63.3	NA	NA	100.0	0.0	NA	NA
Williamson (107)	United Kingdom	1991	English	176	56.0	NA	NA	100.0	0.0	NA	10.2
Attwood (88)	United Kingdom	1992	English	45	66.6	51.1	48.9	100.0	0.0	NA	NA
Bartelsman (90)	Netherlands	1992	English	50	NA	NA	NA	NA	NA	NA	NA
Iftikhar (83)	United Kingdom	1992	English	102	462	63.0	60.8	39.2	100	NA	2.0
Sanchez Robles (118)	Spain	1995	Spanish	13	63.2	NA	NA	100.0	0.0	100.0	NA
Komorowski† (98)	United States	1996	English	14	56.0	78.6	21.4	NA	NA	78.6	50.0
Wright† (108)	United Kingdom	1996	English	166	NA	65.1	34.9	NA	NA	NA	NA
Yuones† (109)	United States	1997	English	61	NA	NA	NA	NA	NA	100.0	NA
Katz (97)	United States	1998	English	102	63.0	82.4	15.7	100.0	0.0	100.0	4.9
Streitz (104)	United States	1998	English	136	NA	NA	NA	NA	NA	NA	NA
Teodori† (45)	Italy	1998	English	30	53.0	60.0	40.0	NA	NA	100.0	NA
Bujanda Fernandez (116)	Spain	1999	Spanish	46	58.0	71.7	28.3	100.0	0.0	NA	NA
Wilkinson† (120)	United Kingdom	1999	English	12	NA	NA	NA	100.0	0.0	25.0	NA
Bani-Hani (89)	United Kingdom	2000	English	357	63.0	58.0	42.0	NA	NA	86.0	NA
Macdonald† (76)	United Kingdom	2000	English	143	57.0	60.1	52.5	100.0	0.0	NA	NA
Rana (101)	United Kingdom	2000	English	44	58.0	72.7	27.3	100.0	0.0	68.2	NA
Rudolph† (102)	United States	2000	English	235	NA	NA	NA	70.6	29.4	100.0	48.5
Conio† (74)	United States	2001	English	154	59.9	81.3	18.7	64.5	35.5	100.0	9.6
Eckardt (75)	Germany	2001	English	60	61.0	58.3	41.7	100.0	0.0	NA	0.0
Fitzgerald (95)	United Kingdom	2001	English	96	62.0	74.0	26.0	NA	NA	70.8	NA
Spechler (103)	United States	2001	English	108	58.0	NA	NA	NA	NA	NA	NA
Srinivasan† (119)	United States	2001	English	8	60.0	NA	NA	NA	NA	100.0	NA
Conio (77)	Italy	2003	English	166	62.3	70.1	29.9	76.0	24.0	NA	45.0
Hillman† (80)	Australia	2003	English	351	59.2	70.9	29.1	NA	NA	100.0	16.0
Hurschler (79)	Switzerland	2003	English	207	NA	NA	NA	NA	NA	36.2	6.3
Murray† (78)	United Kingdom	2003	English	2,950	NA	NA	NA	NA	NA	NA	5.8
Parrilla (100)	Spain	2003	English	43	50.0	76.7	23.3	NA	NA	90.7	7.0
Basu† (91)	United Kingdom	2004	English	135	62.1	NA	NA	94.8	12.6	100.0	7.4
Hage (96)	Netherlands	2004	English	105	63.4	55.2	44.8	100.0	0.0	100.0	10.5
Meining† (99)	Germany	2004	English	148	55.8	53.0	47.0	NA	NA	NA	NA
Solaymani-Dodaran (84)	United Kingdom	2004	English	1,656	63.6	61.6	38.4	NA	NA	NA	NA
Aldulaimi† (87)	United Kingdom	2005	English	126	63.0	76.2	23.8	NA	NA	NA	NA
Dulai† (94)	United States	2005	English	575	60.0	99.0	0.2	NA	NA	100.0	23.3
Murphy (86)	United Kingdom	2005	English	178	57.0	71.4	28.7	81.5	18.5	100.0	18.5
Oberg (85)	Sweden	2005	English	140	57.3	74.3	25.7	100.0	0.0	100.0	0.0
Gladman (112)	United Kingdom	2006	English	195	62.6	55.4	44.6	89.7	10.3	100.0	0.0
Remes-Troche (113)	Mexico	2006	Spanish	185	55.1	56.8	44.3	NA	NA	100.0	NA
Sharma (114)	United States	2006	English	618	59.0	NA	NA	NA	NA	100.0	56.0
Veith† (115)	Germany	2006	English	748	60.9	67.8	32.2	42.1	32.9	100.0	NA

* LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus; SIM, specialized intestinal metaplasia; LGD, low-grade dysplasia; NA, nonapplicable because data were either not available or could not be calculated after exclusion of early incident cancer or high-grade dysplasia at baseline.

† Number of patients, person-years of follow-up, number of cancers, and cancer incidence may differ from published figures because early incident cancers, patients with high-grade-dysplasia at baseline, and associated person-years of risk were excluded where possible.
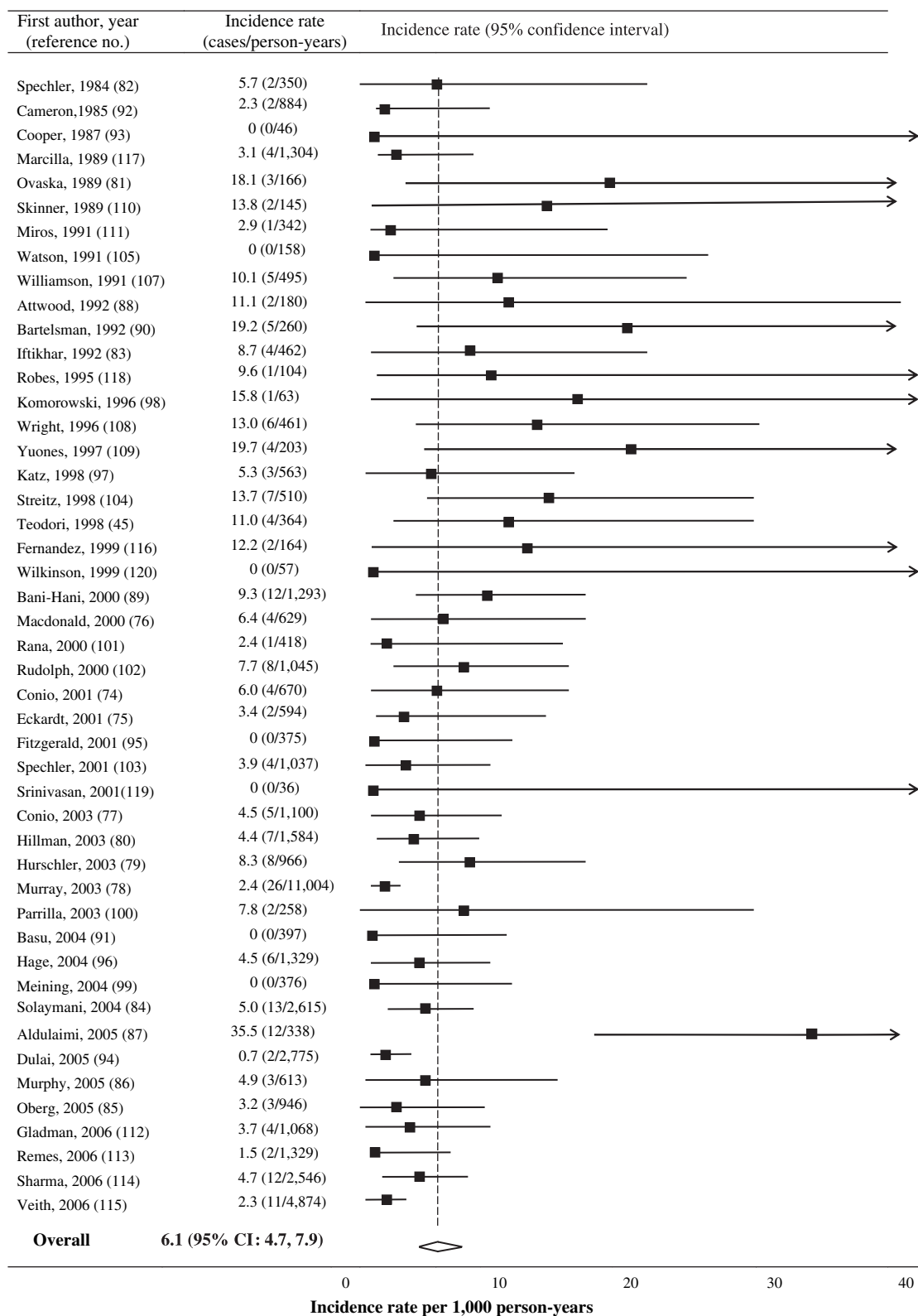
First author, year (reference no.)	Incidence rate (cases/person-years)	Incidence rate (95% confidence interval)
Spechler, 1984 (82)	5.7 (2/350)	
Cameron, 1985 (92)	2.3 (2/884)	
Cooper, 1987 (93)	0 (0/46)	
Marcilla, 1989 (117)	3.1 (4/1,304)	
Ovaska, 1989 (81)	18.1 (3/166)	
Skinner, 1989 (110)	13.8 (2/145)	
Miros, 1991 (111)	2.9 (1/342)	
Watson, 1991 (105)	0 (0/158)	
Williamson, 1991 (107)	10.1 (5/495)	
Attwood, 1992 (88)	11.1 (2/180)	
Bartelsman, 1992 (90)	19.2 (5/260)	
Iftikhar, 1992 (83)	8.7 (4/462)	
Robes, 1995 (118)	9.6 (1/104)	
Komorowski, 1996 (98)	15.8 (1/63)	
Wright, 1996 (108)	13.0 (6/461)	
Yuones, 1997 (109)	19.7 (4/203)	
Katz, 1998 (97)	5.3 (3/563)	
Streitz, 1998 (104)	13.7 (7/510)	
Teodori, 1998 (45)	11.0 (4/364)	
Fernandez, 1999 (116)	12.2 (2/164)	
Wilkinson, 1999 (120)	0 (0/57)	
Bani-Hani, 2000 (89)	9.3 (12/1,293)	
Macdonald, 2000 (76)	6.4 (4/629)	
Rana, 2000 (101)	2.4 (1/418)	
Rudolph, 2000 (102)	7.7 (8/1,045)	
Conio, 2001 (74)	6.0 (4/670)	
Eckardt, 2001 (75)	3.4 (2/594)	
Fitzgerald, 2001 (95)	0 (0/375)	
Spechler, 2001 (103)	3.9 (4/1,037)	
Srinivasan, 2001 (119)	0 (0/36)	
Conio, 2003 (77)	4.5 (5/1,100)	
Hillman, 2003 (80)	4.4 (7/1,584)	
Hurschler, 2003 (79)	8.3 (8/966)	
Murray, 2003 (78)	2.4 (26/11,004)	
Parrilla, 2003 (100)	7.8 (2/258)	
Basu, 2004 (91)	0 (0/397)	
Hage, 2004 (96)	4.5 (6/1,329)	
Meining, 2004 (99)	0 (0/376)	
Solaymani, 2004 (84)	5.0 (13/2,615)	
Aldulaimi, 2005 (87)	35.5 (12/338)	
Dulai, 2005 (94)	0.7 (2/2,775)	
Murphy, 2005 (86)	4.9 (3/613)	
Oberg, 2005 (85)	3.2 (3/946)	
Gladman, 2006 (112)	3.7 (4/1,068)	
Remes, 2006 (113)	1.5 (2/1,329)	
Sharma, 2006 (114)	4.7 (12/2,546)	
Veith, 2006 (115)	2.3 (11/4,874)	
Overall	**6.1 (95% CI: 4.7, 7.9)**	

Incidence rate per 1,000 person-years

FIGURE 2. Forest plot of random-effects meta-analysis of the incidence of cancer in Barrett's esophagus. CI, confidence interval.
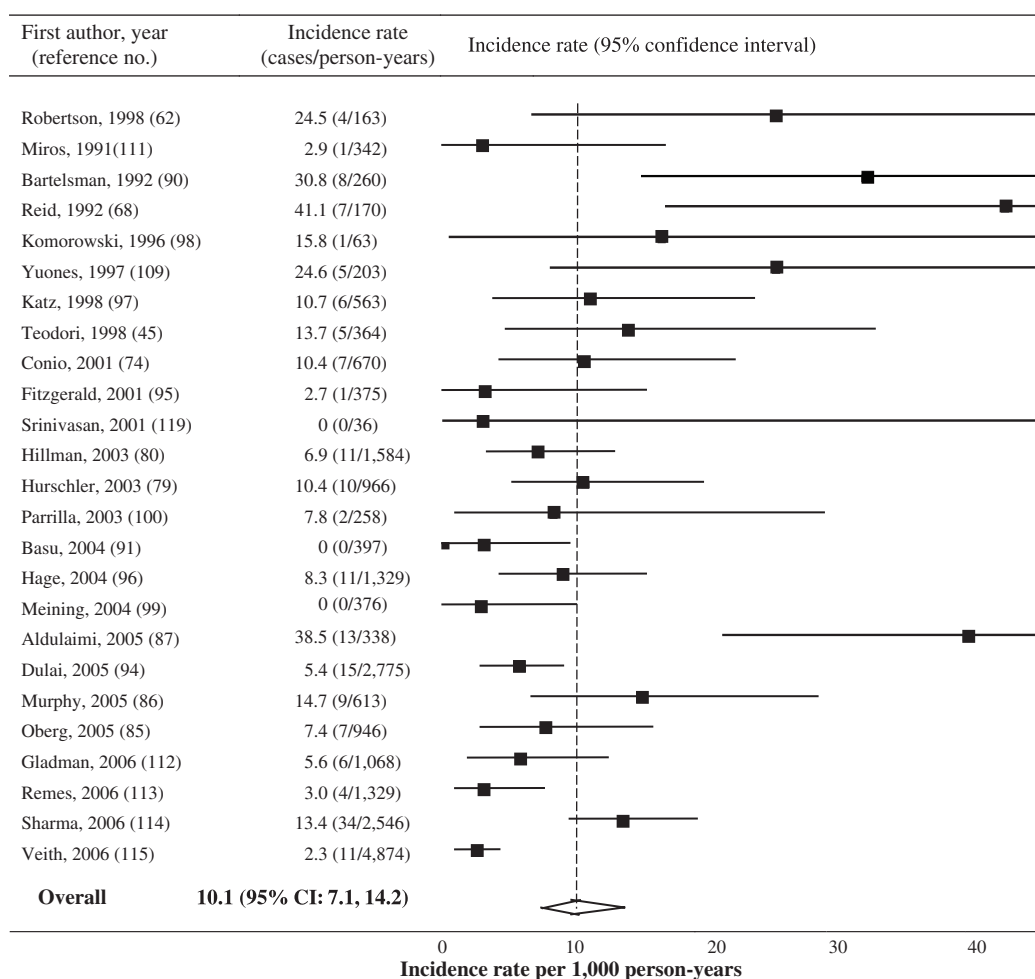
First author, year (reference no.)	Incidence rate (cases/person-years)	Incidence rate (95% confidence interval)
Robertson, 1998 (62)	24.5 (4/163)	
Miros, 1991(111)	2.9 (1/342)	
Bartelsman, 1992 (90)	30.8 (8/260)	
Reid, 1992 (68)	41.1 (7/170)	
Komorowski, 1996 (98)	15.8 (1/63)	
Yuones, 1997 (109)	24.6 (5/203)	
Katz, 1998 (97)	10.7 (6/563)	
Teodori, 1998 (45)	13.7 (5/364)	
Conio, 2001 (74)	10.4 (7/670)	
Fitzgerald, 2001 (95)	2.7 (1/375)	
Srinivasan, 2001 (119)	0 (0/36)	
Hillman, 2003 (80)	6.9 (11/1,584)	
Hurschler, 2003 (79)	10.4 (10/966)	
Parrilla, 2003 (100)	7.8 (2/258)	
Basu, 2004 (91)	0 (0/397)	
Hage, 2004 (96)	8.3 (11/1,329)	
Meining, 2004 (99)	0 (0/376)	
Aldulaimi, 2005 (87)	38.5 (13/338)	
Dulai, 2005 (94)	5.4 (15/2,775)	
Murphy, 2005 (86)	14.7 (9/613)	
Oberg, 2005 (85)	7.4 (7/946)	
Gladman, 2006 (112)	5.6 (6/1,068)	
Remes, 2006 (113)	3.0 (4/1,329)	
Sharma, 2006 (114)	13.4 (34/2,546)	
Veith, 2006 (115)	2.3 (11/4,874)	
Overall	**10.1 (95% CI: 7.1, 14.2)**	

Incidence rate per 1,000 person-years

FIGURE 3. Forest plot of random-effects meta-analysis of the incidence of cancer and high-grade dysplasia in Barrett's esophagus. CI, confidence interval.

Application of quality criteria

Table 2 also shows the pooled cancer incidence after applying the quality criteria: study size greater than 500 person-years, low likelihood of selection bias, and a robust definition of Barrett's esophagus applied. When only those studies including 500 person-years or more were considered, the pooled incidence was 4.4 per 1,000 person-years and the combined high-grade dysplasia and cancer incidence was 7.4 (95 percent CI: 5.3, 10.3) per 1,000 person-years. The same estimate of cancer risk (4.4 per 1,000 person-years) was also obtained when only those studies applying a robust definition of Barrett's esophagus were included, while the combined high-grade dysplasia and cancer incidence was 9.5 (95 percent CI: 6.0, 15.0) per 1,000 person-years. A pooled cancer estimate of 4.9 per 1,000 person-years (incidence of 8.5, 95 percent CI: 5.6, 12.7 per 1,000 person-years for cancer and high-grade dysplasia) was produced when only those studies with less likelihood of selection bias were included. Only eight studies met all three

quality criteria, and the pooled estimate of cancer incidence was 3.9 per 1,000 person-years. Seven studies meeting all three quality criteria gave a pooled estimate for both cancer and high-grade dysplasia of 7.7 (95 percent CI: 4.7, 12.7) per 1,000 person-years. The heterogeneity in the subgroup analysis was substantially lower than in the overall analysis.

Publication bias

A funnel plot is shown in figure 4. Although tests of funnel plot asymmetry were not statistically significant (Begg's test, $p = 0.24$; Egger's test, $p = 0.92$), the funnel plot displayed some evidence of larger, more extreme estimates in the smaller studies, which would be consistent with publication bias. This finding is consistent with the smaller incidence rate noted in the larger studies described in table 2. Publication bias was also assessed by Begg's and Egger's test among studies from different geographic areas, and there was no evidence of publication bias within the US, United Kingdom, or European studies.

TABLE 2.   Pooled estimates of cancer incidence in subgroups and when quality criteria were applied*

Variable	No. of studies	No. of person-years	No. of cancers	Cancer incidence/ 1,000 person-years	95% CI†	χ^2 (df)	p value	I^2 (%)	95% CI
Overall incidence	47	47,496	209	6.1	4.7, 7.9	135.4 (46)	<0.001	66	55, 75
Men	6	3,445.9	31	10.2	6.3, 16.4	7.58 (5)	0.18	34.4	0, 74
Women	5	1,901	7	4.5	2.2, 9.2	2.2 (4)	0.69	0	0, 50
LSBE†	26	11,201.7	61	6.7	5.2, 8.6	23.3 (25)	0.55	0	0, 52
SSBE†	6	1,361.6	7	6.1	3.1, 12.2	0.66 (5)	0.98	0	0, 0
SIM†-positive cases	20	19,716.39	69	4.7	3.3, 6.5	33.3 (19)	0.02	43	3, 66
Application of quality criteria									
Study size (person-years)									
≥500	23	41,278.8	152	4.4	3.4, 5.7	48.5 (22)	0.001	55	27, 72
<500	24	6,217.43	57	11.6	8.4, 16.0	30.1 (23)	0.12	26	0, 55
Possible selection bias‡									
No	28	36,177.1	137	4.9	3.9, 6.3	47.39 (27)	0.09	43	11, 64
Yes	19	11,319.1	72	8.2	5.3, 12.8	53.14 (18)	<0.001	66	45, 79
Definition of Barrett's esophagus									
Well defined§	14	17,570	71	4.4	3.5, 5.6	12.79 (13)	0.46	0	0, 4
Other	33	29,926.23	138	7.0	4.9, 9.9	113.0 (32)	<0.001	72	60, 80
All three quality criteria met¶	8	13,677.8	51	3.9	3.0, 5.2	4.53 (7)	0.72	0	0, 63

* Analyses were not restricted to studies in which early incident cancers or patients with high-grade dysplasia at baseline could be excluded.
† CI, confidence interval; LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus; SIM, specialized intestinal metaplasia.
‡ Selection bias was considered likely if <70% of Barrett's esophagus patients in the center/population were followed up in the study.
§ Endoscopically visible segment and histologically confirmed SIM.
¶ Person-years >500, no selection bias, and well-defined Barrett's esophagus.

DISCUSSION

This systematic review showed that the overall estimate of cancer incidence in Barrett's esophagus was 6.1 cases per 1,000 person-years (0.61 percent per year or 1 in 164 person-years). This incidence is slightly higher than that
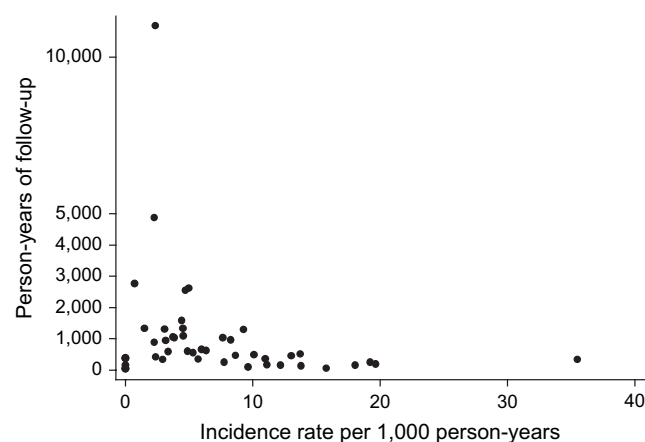
FIGURE 4. Funnel plot of incidence rate against person-years of follow-up.

reported by Shaheen et al. (17), who used a different approach to estimate cancer incidence. It is similar to that observed in the medically treated Barrett's esophagus group in a recent review (18) that compared cancer incidence in medically and surgically treated patients, and it is slightly lower than that reported in the most recently published review (19). However, only one of these reviews excluded early incident cancers and none excluded cancers occurring in patients with high-grade dysplasia at baseline, which will inflate the risk of cancer for patients with uncomplicated Barrett's esophagus. When we limited our analysis to studies in which these two groups were excluded, the cancer incidence was 4.1 per 1,000 person-years (0.41 percent per year or 1 in 244 person-years), which is likely to be a more robust estimate of the cancer incidence in Barrett's esophagus patients.

The occurrence of high-grade dysplasia is an important outcome in Barrett's surveillance programs because its detection provides an opportunity to prevent progression to invasive cancer through esophagectomy (121) or other interventions, such as photodynamic therapy (122) and endoscopic mucosal resection (123). We therefore calculated a combined incidence of cancer and high-grade dysplasia. The pooled estimate of cancer and high-grade dysplasia incidence was 10.0 per 1,000 person-years of follow-up, declining to 9.1 per 1,000 (1 in 110 person-years or 0.91

percent per year) when early incident cancers (or high-grade dysplasia) or cancers occurring in patients with high-grade dysplasia at baseline were excluded. The later incidence is similar to that reported by Thomas et al. (19) even though cancers occurring in patients with high-grade dysplasia at baseline were not excluded.

The quality of the published studies included in this review was highly variable. We considered a number of parameters as quality criteria and decided to apply study size, likelihood of selection bias, and application of a robust definition of Barrett's esophagus. However, because many of the studies were small, did not apply robust criteria for Barrett's esophagus diagnosis, had low follow-up rates, or did not provide information to enable the reader to assess the proportion of patients who were followed up, we undertook subgroup analyses on the basis of these criteria rather than excluding lower-quality studies. Cancer incidence was much lower in large rather than small studies: 4.4 per 1,000 person-years in studies with 500 person-years or more compared with 11.6 per 1,000 in smaller studies. This finding is similar to that of Thomas et al. (19), who reported a low incidence of 5 per 1,000 person-years when they excluded studies with less than 200 person-years.

Three explanations for this finding are possible. First, smaller studies may have included a biased selection of Barrett's esophagus patients with a high cancer risk (e.g., patients referred to specialist treatment centers). Second, large studies may not have been able to identify all incident cases of cancer. Third, there may have been bias against the publication of small studies showing low cancer incidence, but there was little evidence of publication bias in this study. Similarly, studies achieving high follow-up rates or using a robust definition of Barrett's esophagus reported lower cancer incidence than other studies did. Only eight studies met all three quality criteria (seven of which included high-grade dysplasia as an outcome); cancer incidence in these studies was 3.9 per 1,000 person-years, while cancer and high-grade dysplasia incidence was 7.7 per 1,000 person-years. Although these data are from few studies, the studies were large (including almost 14,000 person-years in total and 51 incident cancers) and well performed. Therefore, they are most likely to provide the best estimate of the true incidence of cancer and high-grade dysplasia in uncomplicated Barrett's esophagus.

Information was not available to calculate the incidence in SIM-negative Barrett's esophagus, but, surprisingly, the pooled incidence of cancer in SIM-positive cases (4.7 per 1,000 person-years) was lower than that in all studies (6.1 per 1,000 person-years), which will have included patients without SIM. This may have occurred because the studies providing information regarding SIM status were, in general, large (14 of 20 studies included 500 or more person-years) and provided sufficient information to exclude early incident cancers (18 of 20 studies), thereby resulting in a lower incidence compared with all studies combined.

Few studies provided data to calculate cancer incidence for men and women. However, in the studies that did provide these data, cancer incidence in men was more than twice that in women, which is in keeping with the male predominance among patients with esophageal adenocarci-noma (1, 124) and with studies that show male sex to be a risk factor for progression to cancer (33, 125). We did not find any geographic variation in cancer incidence in Barrett's esophagus. Geographic differences in the population incidence of esophageal adenocarcinoma are well described (2, 5), including a higher incidence in the United Kingdom compared with the United States. Jankowski et al. (126) have suggested that this finding was due to a higher rate of progression from Barrett's esophagus to esophageal adenocarcinoma in the United Kingdom, but our findings do not support this hypothesis. Thomas et al. (19) also reported no geographic variation in Barrett's esophagus cancer risk.

Previous studies (54, 83, 127, 128) indicate that patients with LSBE are at a higher risk of developing cancer than patients with SSBE. In contrast, this review showed no difference in the overall cancer incidence between patients with LSBE or SSBE. However, only six studies provided data to calculate the incidence of cancer in SSBE, and these studies included 1,400 person-years and only seven incident cancers. Our study cannot therefore conclude, with any certainty, that there is no difference in cancer incidence between SSBE and LSBE. The study by Thomas et al. (19) showed a trend toward lower incidence in patients with SSBE, but this analysis was also based on data from a small number of studies.

The funnel plot shows some evidence of publication bias, but the Egger's and Begger's tests were not statistically significant. This finding was in keeping with those of Thomas et al. (19). Conversely, Shaheen et al. (17) concluded that publication bias was present in their review. Inclusion of foreign language papers, more recent publications, and several earlier references that Shaheen et al. did identify may explain the difference in the findings of our review and that of Shaheen et al. There was substantial heterogeneity between studies included in our review, with the risk of esophageal cancer in individual studies varying between 0 and 35.5 cases per 1,000 person-years and an I^2 value of 66 for the combined estimate of cancer incidence. Many factors may have contributed to this heterogeneity, including temporal difference in the studies, study size, proportion of Barrett's esophagus patients followed up, geographic location of studies, definitions of Barrett's esophagus used, and age and distribution of patients. Because of an evident heterogeneity, we applied random-effects models and undertook subgroup analyses where possible, based on the quality criteria. Heterogeneity was substantially reduced in the subgroup analyses, and the results of these analyses may therefore be more reliable.

When data from only the high-quality studies were analyzed, a low incidence of esophageal adenocarcinoma in Barrett's esophagus was found, at 3.9 per 1,000 person-years; the combined incidence of esophageal adenocarcinoma and high-grade dysplasia was somewhat higher at 7.7 per 1,000 person-years. Published data indicate that 19–59 percent of cases of high-grade dysplasia progress to cancer (129). If 40 percent of the incident high-grade dysplasia cases in the studies do not progress to cancer, then the overall risk of cancer in Barrett's esophagus can be estimated to be 6.3 per 1,000 person-years (0.63 percent per year).

To date, we know of no randomized controlled trials of Barrett's esophagus surveillance that have been published,

so several authors have used mathematical models to explore the cost-effectiveness of surveillance (16, 130, 131). Despite different modeling approaches and the application of different costs, these studies confirm that the cost-effectiveness of surveillance is crucially dependent on the incidence of cancer in Barrett's esophagus. On the basis of costs in the United States, Provenzale et al. (16) concluded that, for a cancer risk of 5 per 1,000 person-years, surveillance every 4 years was indicated and, if the risk was 0.4 percent year, surveillance every 5 years was the only strategy that increases quality of life. Modeling surveillance from a United Kingdom perspective, Garside et al. (131) concluded that, at a cancer risk equivalent to 0.5 percent per year, no surveillance costs less and results in a better quality of life than surveillance, irrespective of the surveillance interval used. The estimates of cancer incidence obtained from this systematic review are close to those used in these models and clearly indicate that the cost-effectiveness of Barrett's surveillance is questionable unless it can be targeted to those Barrett's esophagus patients who are at the highest risk of cancer.

In conclusion, this study showed substantial heterogeneity between the published reports that have examined the risk of cancer or high-grade dysplasia in Barrett's esophagus. Men progressed to cancer at twice the rate of women, but no clear difference was found in the rate of progression for patients with SSBE or LSBE, and no geographic variation in progression to cancer was evident. When high-quality studies were examined, the rates of progression to cancer or cancer and high-grade dysplasia combined were low (0.39 percent per year and 0.77 percent per year, respectively), which calls into question the cost-effectiveness of endoscopic surveillance of Barrett's esophagus.

REFERENCES

1. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:1287–9.
2. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83:2049–53.
3. Bytzer P, Christensen PB, Damkier P, et al. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. Am J Gastroenterol 1999;94:86–91.
4. Vizcaino AP, Moreno V, Lambert R, et al. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. Int J Cancer 2002; 99:860–8.
5. Botterweck AA, Schouten LJ, Volovics A, et al. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000;29: 645–54.
6. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999;26(suppl 15):2–8.
7. Spechler SJ, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. Gastroenterology 1996;110:614–21.
8. Stein HJ, Siewert JR. Barrett's esophagus: pathogenesis, epidemiology, functional abnormalities, malignant degeneration, and surgical management. Dysphagia 1993;8: 276–88.
9. Sundelof M, Ye W, Dickman PW, et al. Improved survival in both histologic types of oesophageal cancer in Sweden. Int J Cancer 2002;99:751–4.
10. Polednak AP. Trends in survival for both histologic types of esophageal cancer in US Surveillance, Epidemiology and End Results areas. Int J Cancer 2003;105:98–100.
11. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1998;93:1028–32.
12. Smith AM, Maxwell-Armstrong CA, Welch NT, et al. Surveillance for Barrett's oesophagus in the UK. Br J Surg 1999; 86:276–80.
13. Corley DA, Levin TR, Habel LA, et al. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. Gastroenterology 2002;122:633–40.
14. Duhaylongsod FG, Wolfe WG. Barrett's esophagus and adenocarcinoma of the esophagus and gastroesophageal junction. J Thorac Cardiovasc Surg 1991;102:36–41; discussion 41–2.
15. Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? J Thorac Cardiovasc Surg 1993;105:383–7.
16. Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. Am J Gastroenterol 1999;94:2043–53.
17. Shaheen NJ, Crosby MA, Bozymski EM, et al. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000;119:333–8.
18. Chang EY, Morris CD, Seltman AK, et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with Barrett esophagus: a systematic review. Ann Surg 2007; 246:11–21.
19. Thomas T, Abrams KR, De Caestecker JS, et al. Meta analysis: cancer risk in Barrett's oesophagus. Aliment Pharmacol Ther 2007;26:1465–77.
20. Tharavej C, Hagen JA, Peters JH, et al. Predictive factors of coexisting cancer in Barrett's high-grade dysplasia. Surg Endosc 2006;20:439–43.
21. Heitmiller RF, Redmond M, Hamilton SR. Barrett's esophagus with high-grade dysplasia. An indication for prophylactic esophagectomy. Ann Surg 1996;224:66–71.
22. Tseng EE, Wu TT, Yeo CJ, et al. Barrett's esophagus with high grade dysplasia: surgical results and long-term outcome—an update. J Gastrointest Surg 2003;7:164–70.
23. Zaninotto G, Parenti AR, Ruol A, et al. Oesophageal resection for high-grade dysplasia in Barrett's oesophagus. Br J Surg 2000;87:1102–5.

24. Peters JH, Clark GW, Ireland AP, et al. Outcome of adeno-carcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. J Thorac Cardiovasc Surg 1994;108:813–21.

25. Nigro JJ, Hagen JA, DeMeester TR, et al. Occult esophageal adenocarcinoma: extent of disease and implications for effective therapy. Ann Surg 1999;230:433–8; discussion 438–40.

26. Sutton AJ, Abrams KR, Jones DR, et al. Methods for meta-analysis in medical research. Chichester, United Kingdom: John Wiley & Sons, 2000. (Wiley series in probability and statistics).

27. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

28. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

29. Matthews JN, Altman DG, Campbell MJ, et al. Analysis of serial measurements in medical research. BMJ 1990;300:230–5.

30. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

31. Dear K, Begg C. An approach to assessing publication bias prior to performing a meta-analysis. Stat Sci 1992;7:237–45.

32. Caygill CP, Reed PI, Johnston BJ, et al. A single centre's 20 years' experience of columnar-lined (Barrett's) oesophagus diagnosis. Eur J Gastroenterol Hepatol 1999;11:1355–8.

33. Bani-Hani KE, Bani-Hani BK, Martin IG. Characteristics of patients with columnar-lined Barrett's esophagus and risk factors for progression to esophageal adenocarcinoma. World J Gastroenterol 2005;11:6807–14.

34. Vaughan TL, Dong LM, Blount PL, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. Lancet Oncol 2005;6:945–52.

35. Harle IA, Finley RJ, Belsheim M. Management of adeno-carcinoma in a columnar-lined esophagus. Ann Thorac Surg 1985;40:330–6.

36. Hillman LC, Chiragakis L, Shadbolt B, et al. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust 2004;180:387–91.

37. Khoury GA, Bolton J. Age: an important factor in Barrett's oesophagus. Ann R Coll Surg Engl 1989;71:50–3.

38. Lackey C, Rankin RA, Welsh JD. Stricture location in Barrett's esophagus. Gastrointest Endosc 1984;30:331–3.

39. Macdonald CE, Wicks AC, Playford RJ. Ten years' experi-ence of screening patients with Barrett's oesophagus in a university teaching hospital. Gut 1997;41:303–7.

40. Maley CC, Galipeau PC, Li X, et al. The combination of genetic instability and clonal expansion predicts progression to esophageal adenocarcinoma. Cancer Res 2004;64:7629–33.

41. Montgomery E, Bronner MP, Greenson JK, et al. Are ulcers a marker for invasive carcinoma in Barrett's esophagus? Data from a diagnostic variability study with clinical follow-up. Am J Gastroenterol 2002;97:27–31.

42. Naef AP, Savary M, Ozzello L. Columnar lined lower esophagus: an acquired lesion with malignant predisposition. Report on 140 cases of Barrett's esophagus with 12 adeno-carcinomas. J Thorac Cardiovasc Surg 1975;70:826–35.

43. Nandurkar S, Locke GR III, Murray JA, et al. Rates of en-doscopy and endoscopic findings among people with frequent symptoms of gastroesophageal reflux in the community. Am J Gastroenterol 2005;100:1459–65.

44. Reid BJ, Levine DS, Longton G, et al. Predictors of pro-gression to cancer in Barrett's esophagus: baseline histology

45. Teodori L, Gohde W, Persiani M, et al. DNA/protein flow cytometry as a predictive marker of malignancy in dysplasia-free Barrett's esophagus: thirteen-year follow-up study on a cohort of patients. Cytometry 1998;34:257–63.

46. Voutilainen ME, Juhola MT. The changing epidemiology of esophageal cancer in Finland and the impact of the surveil-lance of Barrett's esophagus in detecting esophageal adeno-carcinoma. Dis Esophagus 2005;18:221–5.

47. Montgomery E, Goldblum JR, Greenson JK, et al. Dysplasia as a predictive marker for invasive carcinoma in Barrett esophagus: a follow-up study based on 138 cases from a diagnostic variability study. Hum Pathol 2001;32:379–88.

48. Burke AP, Sobin LH, Shekitka KM, et al. Dysplasia of the stomach and Barrett esophagus: a follow-up study. Mod Pathol 1991;4:336–41.

49. Burdiles P, Csendes A, Smok G, et al. Progression from in-testinal metaplasia to adenocarcinoma in Barrett's esophagus: usefulness of endoscopic surveillance. Rev Med Chil 2003;131:587–96.

50. Ollyo JB, Savary M, Gonvers JJ, et al. Barrett's esophagus. Retrospective study of 258 cases. Schweiz Med Wochenschr 1985;115:996–7.

51. Drewitz DJ, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. Am J Gastroenterol 1997;92:212–15.

52. Hameeteman W, Tytgat GN, Houthoff HJ, et al. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology 1989;96(5 pt 1):1249–56.

53. van der Burgh A, Dees J, Hop WC, et al. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. Gut 1996;39:5–8.

54. O'Connor JB, Falk GW, Richter JE. The incidence of ade-nocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. Am J Gastroenterol 1999;94:2037–42.

55. Bonelli L. Barrett's esophagus: results of a multicentric sur-vey. G.O.S.P.E. (Gruppo Operativo per lo Studio delle Pre-cancerosi Esofagee). Endoscopy 1993;25:652–4.

56. Weston AP, Krmpotich PT, Cherian R, et al. Prospective long-term endoscopic and histological follow-up of short segment Barrett's esophagus: comparison with traditional long segment Barrett's esophagus. Am J Gastroenterol 1997;92:407–13.

57. Achkar E, Carey W. The cost of surveillance for adenocar-cinoma complicating Barrett's esophagus. Am J Gastroen-terol 1988;83:291–4.

58. Bonelli L, Conio M, Aste H. Risk of adenocarcinoma in Barrett's esophagus: a multicentric study; Le risque d'ad-enocarcinome sur oesophage de Barrett: résultat d'une étude multicentrique. (Published in English and in French). Acta Endosc 1992;22:119–28.

59. Falk GW, Thota PN, Richter JE, et al. Barrett's esophagus in women: demographic features and progression to high-grade dysplasia and cancer. Clin Gastroenterol Hepatol 2005;3:1089–94.

60. Ferraris R, Bonelli L, Conio M, et al. Incidence of Barrett's adenocarcinoma in an Italian population: an endoscopic surveillance programme. Eur J Gastroenterol Hepatol 1997;9:881–5.

61. Nilsson J, Skobe V, Johansson J, et al. Screening for oeso-phageal adenocarcinoma: an evaluation of a surveillance program for columnar metaplasia of the oesophagus. Scand J Gastroenterol 2000;35:10–16.

62. Robertson CS, Mayberry JF, Nicholson DA, et al. Value of endoscopic surveillance in the detection of neoplastic change in Barrett's oesophagus. Br J Surg 1988;75:760–3.

63. Sharma P, Morales TG, Bhattacharyya A, et al. Dysplasia in short-segment Barrett's esophagus: a prospective 3-year follow-up. Am J Gastroenterol 1997;92:2012–16.

64. Sharma P, Weston AP, Morales T, et al. Relative risk of dysplasia for patients with intestinal metaplasia in the distal oesophagus and in the gastric cardia. Gut 2000;46:9–13.

65. Van der Veen AH, Dees J, Blankensteijn JD, et al. Adenocarcinoma in Barrett's oesophagus: an overrated risk. Gut 1989;30:14–18.

66. Weston AP, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic, and histological factors predictive of the development of Barrett's multifocal high-grade dysplasia or adenocarcinoma. Am J Gastroenterol 1999;94:3413–19.

67. Ortiz A, Martinez de Haro LF, Parrilla P, et al. Conservative treatment versus antireflux surgery in Barrett's oesophagus: long-term results of a prospective study. Br J Surg 1996;83:274–8.

68. Reid BJ, Blount PL, Rubin CE, et al. Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. Gastroenterology 1992;102(4 pt 1):1212–19.

69. Chao DL, Maley CC, Wu X, et al. Mutagen sensitivity and neoplastic progression in patients with Barrett's esophagus: a prospective analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1935–40.

70. Cooper BT, Chapman W, Neumann CS, et al. Continuous treatment of Barrett's oesophagus patients with proton pump inhibitors up to 13 years: observations on regression and cancer incidence. Aliment Pharmacol Ther 2006;23:727–33.

71. Guardino JM, Khandwala F, Lopez R, et al. Barrett's esophagus at a tertiary care center: association of age on incidence and prevalence of dysplasia and adenocarcinoma. Am J Gastroenterol 2006;101:2187–93.

72. Wesdorp IC, Bartelsman J, Schipper ME, et al. Effect of long-term treatment with cimetidine and antacids in Barrett's oesophagus. Gut 1981;22:724–7.

73. Cooper BT, Neumann CS, Cox MA, et al. Continuous treatment with omeprazole 20 mg daily for up to 6 years in Barrett's oesophagus. Aliment Pharmacol Ther 1998;12:893–7.

74. Conio M, Cameron AJ, Romero Y, et al. Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut 2001;48:304–9.

75. Eckardt VF, Kanzler G, Bernhard G. Life expectancy and cancer risk in patients with Barrett's esophagus: a prospective controlled investigation. Am J Med 2001;111:33–7.

76. Macdonald CE, Wicks AC, Playford RJ. Final results from 10 year cohort of patients undergoing surveillance for Barrett's oesophagus: observational study. BMJ 2000;321:1252–5.

77. Conio M, Blanchi S, Lapertosa G, et al. Long-term endoscopic surveillance of patients with Barrett's esophagus. Incidence of dysplasia and adenocarcinoma: a prospective study. Am J Gastroenterol 2003;98:1931–9.

78. Murray L, Watson P, Johnston B, et al. Risk of adenocarcinoma in Barrett's oesophagus: population based study. BMJ 2003;327:534–5.

79. Hurschler D, Borovicka J, Neuweiler J, et al. Increased detection rates of Barrett's oesophagus without rise in incidence of oesophageal adenocarcinoma. Swiss Med Wkly 2003;133:507–14.

80. Hillman LC, Chiragakis L, Clarke AC, et al. Barrett's esophagus: macroscopic markers and the prediction of dysplasia and adenocarcinoma. J Gastroenterol Hepatol 2003;18:526–33.

81. Ovaska J, Miettinen M, Kivilaakso E. Adenocarcinoma arising in Barrett's esophagus. Dig Dis Sci 1989;34:1336–9.

82. Spechler SJ, Robbins AH, Rubins HB, et al. Adenocarcinoma and Barrett's esophagus. An overrated risk? Gastroenterology 1984;87:927–33.

83. Iftikhar SY, James PD, Steele RJC, et al. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. Gut 1992;33:1155–8.

84. Solaymani-Dodaran M, Logan RF, West J, et al. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. Gut 2004;53:1070–4.

85. Oberg S, Wenner J, Johansson J, et al. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. Ann Surg 2005;242:49–54.

86. Murphy SJ, Dickey W, Hughes D, et al. Surveillance for Barrett's oesophagus: results from a programme in Northern Ireland. Eur J Gastroenterol Hepatol. 2005;17:1029–35.

87. Aldulaimi DM, Cox M, Nwokolo CU, et al. Barrett's surveillance is worthwhile and detects curable cancers. A prospective cohort study addressing cancer incidence, treatment outcome and survival. Eur J Gastroenterol Hepatol 2005;17:943–50.

88. Attwood SEA, Barlow AP, Norris TL, et al. Barrett's oesophagus: effect of antireflux surgery on symptom control and development of complications. Br J Surg 1992;79:1050–3.

89. Bani-Hani K, Sue-Ling H, Johnston D, et al. Barrett's oesophagus: results from a 13-year surveillance programme. Eur J Gastroenterol Hepatol 2000;12:649–54.

90. Bartlesman JF, Hameeteman W, Tytgat GN. Barrett's oesophagus. Eur J Cancer Prev 1992;1:323–5.

91. Basu KK, Pick B, de Caestecker JS. Audit of a Barrett's epithelium surveillance database. Eur J Gastroenterol Hepatol 2004;16:171–5.

92. Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. N Engl J Med 1985;313:857–9.

93. Cooper BT, Barbezat GO. Barrett's oesophagus: a clinical study of 52 patients. Q J Med 1987;62:97–108.

94. Dulai GS, Shekelle PG, Jensen DM, et al. Dysplasia and risk of further neoplastic progression in a regional Veterans Administration Barrett's cohort. Am J Gastroenterol 2005;100:775–83.

95. Fitzgerald RC, Saeed IT, Khoo D, et al. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. Dig Dis Sci 2001;46:1892–8.

96. Hage M, Siersema PD, van Dekken H, et al. Oesophageal cancer incidence and mortality in patients with long-segment Barrett's oesophagus after a mean follow-up of 12.7 years. Scand J Gastroenterol 2004;39:1175–9.

97. Katz D, Rothstein R, Schned A, et al. The development of dysplasia and adenocarcinoma during endoscopic surveillance of Barrett's esophagus. Am J Gastroenterol 1998;93:536–41.

98. Komorowski RA, Hogan WJ, Chausow DD. Barrett's ulcer: the clinical significance today. Am J Gastroenterol 1996;91:2310–13.

99. Meining A, Ott R, Becker I, et al. The Munich Barrett follow up study: suspicion of Barrett's oesophagus based on either endoscopy or histology only—what is the clinical significance? Gut 2004;53:1402–7.

100. Parrilla P, Martinez De Haro LF, Ortiz A, et al. Long-term results of a randomized prospective study comparing medical

and surgical treatment of Barrett's esophagus. Ann Surg 2003;237:291–8.

101. Rana PS, Johnston DA. Incidence of adenocarcinoma and mortality in patients with Barrett's oesophagus diagnosed between 1976 and 1986: implications for endoscopic surveillance. Dis Esophagus 2000;13:28–31.

102. Rudolph RE, Vaughan TL, Storer BE, et al. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. Ann Intern Med 2000;132:612–20.

103. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. JAMA 2001;285:2331–8.

104. Streitz JM Jr, Ellis FH Jr, Tilden RL, et al. Endoscopic surveillance of Barrett's esophagus: a cost-effectiveness comparison with mammographic surveillance for breast cancer. Am J Gastroenterol 1998;93:911–15.

105. Watson RGP, Porter KG, Sloan JM. Incidence of adenocarcinoma in Barrett's oesophagus and an evaluation of endoscopic surveillance. Eur J Gastroenterol Hepatol 1991;3:159–62.

106. Williamson WA, Ellis FH Jr, Gibb SP, et al. Effect of antireflux operation on Barrett's mucosa. Ann Thorac Surg 1990;49:537–42.

107. Williamson WA, Ellis FH Jr, Gibb SP, et al. Barrett's esophagus: prevalence and incidence of adenocarcinoma. Arch Intern Med 1991;151:2212–16.

108. Wright TA, Gray MR, Morris AI, et al. Cost effectiveness of detecting Barrett's cancer. Gut 1996;39:574–9.

109. Younes M, Ertan A, Lechago LV, et al. p53 protein accumulation is a specific marker of malignant potential in Barrett's metaplasia. Dig Dis Sci 1997;42:697–701.

110. Skinner DB. The incidence of cancer in Barrett's esophagus varies according to the series. In: Giuli R, McCallum RW, eds. Benign lesions of the esophagus and cancer. New York, NY: Springer-Verlag, 1989:764–5.

111. Miros M, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. Gut 1991;32:1441–6.

112. Gladman L, Chapman W, Iqbal TH, et al. Barrett's oesophagus: an audit of surveillance over a 17-year period. Eur J Gastroenterol Hepatol 2006;18:271–6.

113. Remes-Troche JM, Ramirez-Arias JF, Gomez-Escudero O, et al. Recommended endoscopic surveillance of patients with Barrett's esophagus (BE) is a cost-effective strategy? (In Spanish). Rev Gastroenterol Mex 2006;71:46–54.

114. Sharma P, Falk GW, Weston AP, et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2006;4:566–72.

115. Vieth M, Schubert B, Lang-Schwarz K, et al. Frequency of Barrett's neoplasia after initial negative endoscopy with biopsy: a long-term histopathological follow-up study. Endoscopy 2006;38:1201–5.

116. Bujanda Fernandez de Pierola L, Munoz Villafranca C, Sanchez Martinez A, et al. Adenocarcinoma in Barrett's esophagus. A retrospective study of 46 patients followed during 3.5 years. (In Spanish). An Med Interna 1999;16: 178–80.

117. Garcia Marcilla JA, Parrilla Paricio P, Ortiz Escandell MA, et al. Barrett esophagus: epidemiologic data and risk of becoming malignant. (In Spanish). Rev Esp Enferm Apar Dig 1989;76:419–23.

118. Sanchez Robles C, Santalla Pecina F, Retamero Orta MD. Barrett esophagus. An epidemiological study in an area of Spain. (In Spanish). Rev Esp Enferm Dig 1995;87:353–5.

119. Srinivasan R, Katz PO, Ramakrishnan A, et al. Maximal acid reflux control for Barrett's oesophagus: feasible and effective. Aliment Pharmacol Ther 2001;15:519–24.

120. Wilkinson SP, Biddlestone L, Gore S, et al. Regression of columnar-lined (Barrett's) oesophagus with omeprazole 40 mg daily: results of 5 years of continuous therapy. Aliment Pharmacol Ther 1999;13:1205–9.

121. Williams VA, Watson TJ, Herbella FA, et al. Esophagectomy for high grade dysplasia is safe, curative, and results in good alimentary outcome. J Gastrointest Surg 2007;11:1589–97.

122. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia. Gastrointest Endosc 2007; 66:460–8.

123. Larghi A, Lightdale CJ, Ross AS, et al. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. Endoscopy 2007;39:1086–91.

124. de Jonge PJ, Wolters LM, Steyerberg EW, et al. Environmental risk factors in the development of adenocarcinoma of the oesophagus or gastric cardia: a cross-sectional study in a Dutch cohort. Aliment Pharmacol Ther 2007;26:31–9.

125. de Jonge PJ, Steyerberg EW, Kuipers EJ, et al. Risk factors for the development of esophageal adenocarcinoma in Barrett's esophagus. Am J Gastroenterol 2006;101:1421–9.

126. Jankowski JA, Provenzale D, Moayyedi P. Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. Gastroenterology 2002;122:588–90.

127. Shaheen NJ. Should we worry about the length of Barrett's esophagus? Gastrointest Endosc 2005;62:682–5.

128. Weston AP, Sharma P, Mathur S, et al. Risk stratification of Barrett's esophagus: updated prospective multivariate analysis. Am J Gastroenterol 2004;99:1657–66.

129. Al-Kasspooles MF, Hill HC, Nava HR, et al. High-grade dysplasia within Barrett's esophagus: controversies regarding clinical opinions and approaches. Ann Surg Oncol 2002;9: 222–7.

130. Inadomi JM, Sampliner R, Lagergren J, et al. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. Ann Intern Med 2003;138:176–86.

131. Garside R, Pitt M, Somerville M, et al. Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. Health Technol Assess 2006;10:1–142, iii–iv.