

Preoperative Prevalence of Barrett's Esophagus in Esophageal Adenocarcinoma: A Systematic Review

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Background & Aims: The public health impact of past screening and surveillance practices on the outcomes of Barrett's related cancers has not previously been quantified. Our purpose was to determine the prior prevalence of Barrett's esophagus in reported cases of incident adenocarcinoma undergoing resection, as an indirect measure of impact. **Methods:** We performed a systematic review of the literature from 1966 to 2000. Studies were included if they reported: (1) the number of consecutive adenocarcinomas resected, and (2) the number of those resected who had a previously known diagnosis of Barrett's. We generated summary estimates using a random effects model. **Results:** We identified and reviewed 752 studies. Twelve studies representing a total of 1503 unique cases of resected adenocarcinomas met inclusion criteria. Using a random effects model, the overall percentage of patients undergoing resection who had a prior diagnosis of Barrett's was $4.7\% \pm 2.9\%$. **Conclusions:** The low prior prevalence ($\sim 5\%$) of Barrett's esophagus in this study population provides indirect evidence to suggest that recent efforts to identify patients with Barrett's—whether through endoscopic screening or evaluation of symptomatic patients—have had minimal public health impact on esophageal adenocarcinoma outcomes. The potential benefits of endoscopic surveillance seem to have been limited to only a fraction of those individuals at risk. These data thus provide a clear and compelling rationale for the development of effective screening strategies to identify patients with Barrett's esophagus.

Barrett's esophagus is an epithelial metaplasia occurring in some individuals with chronic gastroesophageal reflux disease (GERD), which carries an increased risk of esophageal adenocarcinoma.^{1,2} In recent decades, the incidence of esophageal and gastric cardia adenocarcinomas in the United States and Western Europe has been increasing at a rapid rate.³ Unfortunately, most esophageal adenocarcinomas are diagnosed at an advanced stage, presumably because tumors remain asymptomatic until they are locally advanced. Data from the

Surveillance, Epidemiology, and End Results (SEER) registry suggest that only one quarter of all esophageal cancers in the United States are diagnosed at an early stage.⁴ Survival is stage dependent, and the $\sim 10\%$ overall 5-year survival rate for esophageal adenocarcinoma in the United States reflects the fact that most esophageal adenocarcinomas are diagnosed at an advanced stage.⁵

Barrett's esophagus is believed to be the precursor lesion for most adenocarcinomas of the esophagus, gastroesophageal junction, and gastric cardia.^{6–9} Progression to cancer may transpire over several years and provides a critical opportunity for healthcare providers to intervene through strategies aimed at the prevention and/or early detection of adenocarcinoma. Surveillance with periodic endoscopic biopsies to detect dysplasia and early-stage cancer is now standard care for patients with Barrett's esophagus.¹⁰ Because Barrett's esophagus is generally believed to represent an acquired response to chronic GERD, endoscopic screening of patients with symptoms of GERD has been proposed to detect prevalent cases of Barrett's, but this is not standard care.¹⁰

Because Barrett's esophagus is itself an asymptomatic condition, and systematic screening of those with GERD is not a routine practice, the diagnosis is generally made fortuitously in those undergoing endoscopy for other reasons. Evidence suggests that the true population prevalence of Barrett's esophagus is many-fold higher than the prevalence of those who have been formally diagnosed.¹¹ Surveillance efforts for the early detection and treatment of esophageal adenocarcinoma have thus been focused on only a small proportion of all those at risk. The public health impact of recent screening and surveillance practices in Barrett's esophagus on esophageal

Abbreviations used in this paper: GERD, gastroesophageal reflux disease; SEER, Surveillance, Epidemiology, and End Results.

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Table 1. Details of Study Selection by Reviewer Number 1

Years of publication	Titles	Abstracts	Papers	Included
1966–1974	4	1	0	0
1975–1979	9	3	0	0
1980–1984	37	7	1	0
1985–1989	101	25	12	1
1990–1994	195	32	12	4
1995–2000	406	29	11	7
Total	752	97	36	12

adenocarcinoma outcomes has not previously been quantified in light of this fact.

Our purpose was to determine the proportion of reported cases of esophageal adenocarcinoma undergoing resection that had a previously known diagnosis of Barrett's esophagus. Our hypothesis was that the public health impact of recent screening and surveillance practices on esophageal adenocarcinoma outcomes has been minimal because only a small proportion of patients undergoing resection were known to have Barrett's esophagus before the diagnosis of their cancer.

Methods

We performed a systematic review of the published English language literature from 1966 to May 2000 to identify observational studies of patient cohorts undergoing resection for high-grade dysplasia or adenocarcinoma of the esophagus, gastroesophageal junction, or gastric cardia. An initial, computerized database search of the English language literature from 1966 to May 2000 was performed using MEDLINE/HealthSTAR (National Library of Medicine, Bethesda, MD). The search strategy combined the keywords "Barrett esophagus," and "adenocarcinoma." We used "adenocarcinoma" as a broad term to include all types of Barrett's associated cancers in our search. All identified titles were reviewed by 2 independent reviewers (G.D. and S.G.) and assessed for relevance. Abstracts corresponding to potentially relevant titles were then retrieved, reviewed, and assessed for relevance. Full-text papers corresponding to potentially relevant abstracts were then retrieved and reviewed, and pertinent data were abstracted using a standardized data collection form.

Studies were included only if they reported the following information: (1) the number of consecutive adenocarcinomas resected (denominator), and (2) the number of those resected who had a known diagnosis of Barrett's esophagus before the diagnosis of adenocarcinoma (numerator). Studies were excluded if they did not report data necessary to determine values for the numerator and denominator.

Data were abstracted from all the full-text articles reviewed. Variables assessed included: time frame studied, year of publication, country of origin, study design (retrospective vs. prospective, population-based vs. selected population), total number of consecutive cases of adenocarcinoma or high-grade

dysplasia presenting during study time frame, total number of consecutive cases of adenocarcinoma or high-grade dysplasia resected during study time frame, and total number of consecutive cases of adenocarcinoma or high-grade dysplasia that underwent resection with a prior diagnosis of Barrett's esophagus during the time frame studied.

Quantitative, pooled, summary estimates of the prior prevalence of Barrett's esophagus across individual studies were made using the fixed effects model of Peto and the random effects model of DerSimonian and Laird.¹² These models differ from a simple arithmetic average in that they attempt to adjust the summary estimate for variability (or uncertainty) that may exist between different studies and/or within a given study. In both models, the summary or "meta" estimate represents a weighted average of results from the individual studies with the assumption of homogeneity across studies. In both approaches, studies with smaller sample sizes have greater variability and are therefore given less weight.

The random effects model differs from the fixed effects model in that the fixed model only uses within study variability to form the weights, whereas the random effects model uses a combination of both within and between study variability to form the weights. This between-study variability component is the same for all studies and depends on how much all of the individual studies vary around the overall prevalence. Because the random effects model allows for both within and between study variability, estimates based on it are considered more conservative. The fixed effects model is, in fact, a special case of the random effects model with the assumption of no between study variability.

Summary estimates were generated using arithmetic, fixed effects, and random effects models. A Pearson correlation coefficient was calculated to describe the relationship between study sample size and the reported percentage of patients undergoing resection who had a prior history of Barrett's esophagus. A test for homogeneity across studies was also performed with a $P < 0.05$ level considered statistically significant.

Results

We identified and reviewed 752 study titles based on our search of MEDLINE/HealthSTAR. Reviewer number 1 selected 36 papers for review, including all 21 papers selected by reviewer number 2 (see Tables 1 and 2). There

Table 2. Details of Study Selection by Reviewer Number 2

Years of publication	Titles	Abstracts	Papers	Included
1966–1974	4	1	0	0
1975–1979	9	2	0	0
1980–1984	37	6	0	0
1985–1989	101	17	5	1
1990–1994	195	14	7	4
1995–2000	406	17	9	7
Total	752	57	21	12

Table 3. Excluded Studies

Author	Clinical setting	Time frame	Number of cases presenting	Number of cases resected	Number of resected with prior diagnosis BE	% resected with prior diagnosis BE
Kuster	La Jolla, CA	1976–1986	NR	48	NR ^a	NR
Ellis	Burlington, MA	1970–1988	NR	190	NR ^a	NR
MacDonald	British Columbia	1977–1983	34	NR	NR ^a	NR
Steiger	Allen Park, MI	1975–1982	11	8	NR ^a	NR
Mitchell	Mt View, CA	1978–1985	NR	40	NR ^a	NR
Rogers	Baltimore, MD	NR	NR	NR ^a	9	NR
Yoshida	Tokyo, Japan	1965–1986	NR	52	NR ^a	NR
Wang	Boston, MA	1975–1982	NR	160	NR ^a	NR
Peters	Los Angeles, CA	1985–1993	NR	NR ^a	17	NR
Lerut	Belgium	1975–1991	NR	NR ^a	19	NR
Wolfe	Durham, NC	1985–1992	NR	93	NR ^a	NR
Streitz	Burlington, MA	1973–1991	NR	NR ^a	19	NR
Moghissi	Cottingham, UK	1971–1991	NR	264	NR ^a	NR
Menke-P	Netherlands	1978–1988	NR	NR ^a	6	NR
Gray	Vancouver, Canada	1977–1987	243	NR	NR ^a	NR
Harvey	Los Angeles, CA	1954–1988	107	NR ^a	1	NR
Hoff	Nashville, TN	1988–1996	NR	70	NR ^a	NR
Chalasanani	Atlanta, GA	1990–1996	NR	NR ^a	8	NR
Collard	Brussels, Belgium	1985–1996	NR	NR ^a	5	NR
Ruol	Padova, Italy	1980–1993	NR	NR ^a	5	NR
Agha	Ann Arbor, MI	1962–1983	174	NR	NR ^a	NR
Levine	Philadelphia, PA	1979–1982	17	NR	NR ^a	NR
Saubier	Lyon, France	1973–1982	NR	NR ^a	10	NR
Harle	Ontario, Canada	1973–1983	NR	NR ^a	2	NR

BE, Barrett's esophagus; NR, not recorded.

^aIndicates primary reason for exclusion of study.

was a 100% concordance between reviewers with regard to final inclusion and exclusion of all studies reviewed based on the 2 predefined inclusion criteria. In total, 24 papers^{13–36} were excluded: 11^{18,21,22,24,26,28,30–32,35,36} because of a missing denominator and 13^{13–17,19,20,23,25,27,29,33,34} because of a missing numerator. Details of studies excluded after review of full-text papers are presented in Table 3.

Twelve studies,^{37–48} representing a total of 1503 unique cases, met both the inclusion criteria. Details of included studies are presented in Table 4. All included studies were conducted in Western Europe (67%) or the

United States (33%) and published between 1988 and 1999. The time frame of these studies ranged from 1970 to 1995. Eleven of the 12 included studies represented selected single-center cohorts, with that from Bytzer et al.³⁷ being the sole population-based cohort study. Ten of the 12 included studies were historical (retrospective) cohort studies, with only Cameron et al.⁴³ and Johansson et al.⁴² reporting prospective data.

The reasons for undergoing resection varied across studies. All studies included cases of esophageal adenocarcinoma. Some studies also included cases with high-

Table 4. Included Studies

Author	Clinical setting	Time frame	Number of cases presenting	Number of cases resected	Number of resected with prior diagnosis BE	% resected with prior diagnosis BE
Bytzer	Denmark	1987–1992	524	200	4	2%
Peracchia	Milan, Italy	1992–1998	218	147	6	4%
Van Sandick	Amsterdam, Netherlands	1993–1996	NR	198	16	8%
Holscher	Munich, Germany	1982–1995	NR	260	8	3%
Thomas	Marseilles, France	1979–1995	NR	164	16	10%
Johansson	Lund, Sweden	1985–1992	NR	54	4	7%
Cameron	Rochester, MN	1994	NR	39	6	15%
Li	Dublin, Ireland	1971–1990	NR	207	2	1%
Moon	Milwaukee, WI	1974–1990	NR	88	8	9%
Ribet	Lille, France	1970–1988	NR	28	2	7%
Duhaylonghsod	Durham, NC	1985–1990	NR	57	5	9%
Hamilton	Baltimore, MD	1980–1986	NR	61	13	21%

BE, Barrett's esophagus; NR, not recorded.

grade dysplasia in Barrett's esophagus. Other studies included patients with cancer of the gastroesophageal junction or gastric cardia. Specifically, 4 of the studies (with a total of 576 unique cases)^{37,40,45,46} included only esophageal adenocarcinomas. In 3 studies (with a total of 300 unique cases),⁴²⁻⁴⁴ 50% of cases were from the gastric cardia or gastroesophageal junction. Five studies^{38,39,41,47,48} included cardia and/or gastroesophageal junction tumors (with a total of 627 unique cases), but did not report the exact number of cases from each anatomic region. The overall proportion of adenocarcinoma cases undergoing resection with a prior diagnosis of Barrett's esophagus varied widely, from 1% to 21%, across the included studies. The *P* value of our test for study homogeneity was $P = 0.075$.

As shown in Figure 1, there was an inverse relationship between sample size and percentage of sample with a prior diagnosis of Barrett's esophagus. The Pearson's correlation coefficient for this relationship was $r = -0.74$, indicating a moderately strong inverse relationship. Figure 1 may also be interpreted as a funnel plot for assessing the possibility of publication bias, with the tip of the funnel pointing to the right.¹²

As shown in Figure 2, there was no discernible relationship between the first year of the study time frame and percentage of sample with a prior diagnosis of Barrett's esophagus ($r = -0.07$). An arithmetic summary of studies, or what might be termed an "equal" effects model, suggested that 6% (median 7%, range, 1%–21%) of all patients undergoing resection had a known prior diagnosis of Barrett's esophagus. Using a fixed effects model, we arrive at a pooled estimate of 3.1% with a standard error of 1.8% for the proportion of patients undergoing resection with a known prior diag-

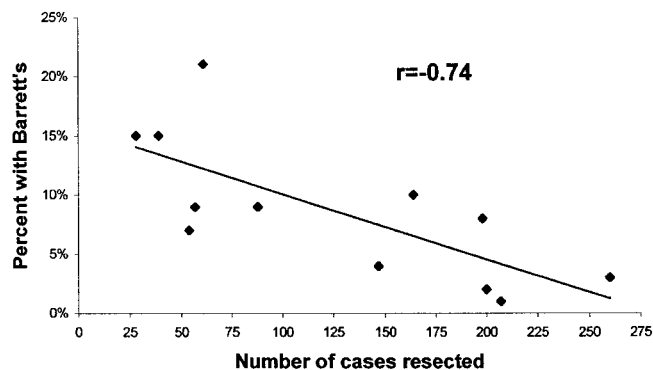


Figure 1. Relationship between study sample size, represented by number of cases resected, and percent of cases resected with a prior diagnosis of Barrett's esophagus. The correlation coefficient of $r = -0.74$ indicates a moderately strong inverse relationship. The line shown is a graphic description of this relationship, or the linear regression line of best fit.

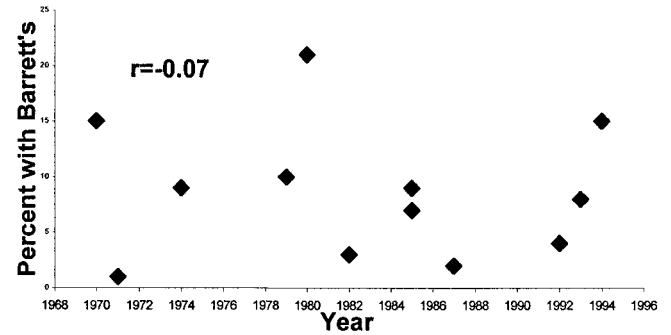


Figure 2. Relationship between first year of study time frame and percentage of reported patients undergoing resection who had a prior diagnosis of Barrett's esophagus. The correlation coefficient of $r = -0.07$ indicates that no relationship exists.

nosis of Barrett's. Using a random effects model, the overall (weighted average) percent of reported patients undergoing resection with a prior diagnosis of Barrett's esophagus was 4.7% with a standard error of 2.9%, based on the results of the 12 studies included in this review. The results of the random effects model are shown graphically in Figure 3.

Only 2 of the 12 studies^{37,38} in this review reported the total number of incident cases of adenocarcinoma (i.e., those who did have surgery as well as those who did not). The total number of cases reported in these series was more than double the number who underwent resection (742 total cases presenting vs. 347 cases resected).

Discussion

Our systematic review suggests that the vast majority of patients reported to have undergone resection for incident esophageal adenocarcinoma were not previously diagnosed with Barrett's esophagus. The implications of this finding are clear. Surveillance of patients with known Barrett's esophagus—although potentially beneficial to those individuals enrolled—has had minimal capacity for impact on esophageal adenocarcinoma outcomes at the population level, because the majority of patients were never diagnosed with Barrett's esophagus and thereby made eligible for surveillance programs. These data suggest that screening programs to identify patients with Barrett's esophagus are a necessary adjunct to surveillance programs.

There are several possible explanations for the low prevalence of previously known Barrett's esophagus among the reported series of those undergoing surgery for incident adenocarcinoma included in this report. This could reflect an incorrect assumption that Barrett's is the precursor to most esophageal adenocarcinomas; incorrect reporting of previously diagnosed Barrett's esophagus in

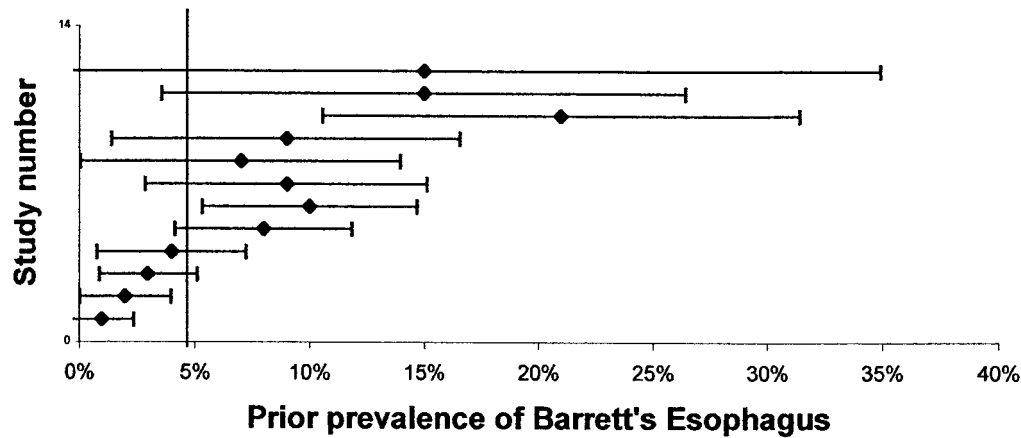


Figure 3. Prior prevalence of Barrett's esophagus among patients undergoing resection for incident adenocarcinoma in the 12 included studies. The black dots with horizontal lines represent point estimates of prior prevalence from each of the individual studies with 95% confidence intervals generated in the random effect model. The vertical line at 4.7% represents the summary estimate of prior prevalence using the random effect model.

the reported studies; or a skewed cohort of patients presenting for surgery. An alternative explanation is that current screening practices to identify patients with Barrett's esophagus are inadequate.

Based on a strong biologic rationale and a wealth of observational evidence, it appears that the majority of esophageal adenocarcinomas do develop in the background of Barrett's esophagus.^{1,2,6-8} Of the 9 studies included in the present article that contained relevant data, the prevalence (as opposed to prior prevalence) of Barrett's esophagus at the time of surgery ranged from 24%⁴⁴ to 64%.^{43,48} Studies that seemed to limit ascertainment bias by conducting a rigorous search for Barrett's in resection specimens tended to give higher estimates of prevalence.^{43,48} Other studies not included in the present review have produced similar estimates. For example, Lagergren et al.⁴⁹ reported a Barrett's prevalence of 69% (118 of 189 cases of esophageal adenocarcinoma) at the time of cancer diagnosis. Even these may be underestimates, as cancer may overgrow the Barrett's segment from which it arose. Thus, it seems likely that Barrett's esophagus is the precursor to most esophageal adenocarcinomas. The studies in this review also included some cases with high-grade dysplasia as the preoperative diagnosis, as well as some with adenocarcinoma of the gastric cardia or gastroesophageal junction. The inclusion of cases with high-grade dysplasia is readily explained by the fact that, in many centers, surgery is routinely performed for high-grade dysplasia because coincident adenocarcinoma is commonly found in the esophagectomy specimen, having been missed at endoscopic surveillance because of a sampling error.⁵⁰ Cancers of the gastric cardia and/or gastroesophageal junction were likely included in many of the series for at least 2 reasons. One is the variation in anatomic definitions and potential for measurement error, which can create difficulty in distinguishing cancer of the esophagus from

cancer in the region of the gastroesophageal junction or cardia.^{37,40,43} Another is the epidemiologic evidence suggesting that these cancers share common risk factors and a similar rate of increasing incidence.^{3,51,52} Furthermore, observational studies suggest that many cardia cancers arise from short segments (i.e., <3 cm) of Barrett's esophagus.^{8,9}

Underreporting of previously diagnosed Barrett's esophagus may have occurred, but seems unlikely given the widely known association between Barrett's and cancer, the importance patients (especially those who present with cancer) attach to having this diagnosis, and the interest investigators have in this condition. If anything, those patients with a prior diagnosis of Barrett's esophagus were likely to be overrepresented among those reported to have undergone surgery in these series because the majority of cases had access to care in referral centers where meticulous routine surveillance may allow early detection of cancer before it overgrows the Barrett's segment. In contrast, screening patients with reflux disease to detect Barrett's esophagus has only recently been formally proposed. Therefore, by far the most likely explanation for the findings in this study is that screening practices to detect Barrett's have heretofore been inadequate, ad hoc, or in certain clinical settings nonexistent.

The strengths and biases of the individual included studies may be obscured by neat summary estimates. Therefore, we considered potential sources of heterogeneity across studies, including: (1) study sample size, (2) time frame of study, (3) ascertainment bias, and (4) study population. The moderately strong ($r = -0.74$) inverse relationship between study sample size and reported percentage of patients with a prior diagnosis of Barrett's esophagus suggests bias. The funnel plot in Figure 1, and test for homogeneity based on this relationship, also suggest that this may represent bias against submitting

and publishing smaller studies in which a low percentage of patients undergoing resection for adenocarcinoma had a previously known diagnosis of Barrett's esophagus.

Studies included in this review describe patients from the 1970s to the 1990s. It is clear that the approach to management of patients with Barrett's esophagus, particularly in regard to screening and surveillance, has undergone substantial change over this time period. However, our findings, as summarized in Figure 2, do not support the potential contention that temporal changes in available evidence and clinical practice have had a substantial impact on the outcome of interest over this time frame.

The rigor with which the prior prevalence of Barrett's esophagus was sought or reported may have varied across the included studies. This variation in case identification, or ascertainment bias, may have led to misclassification and underestimation of the prior prevalence of Barrett's esophagus. In other words, failure to report a prior diagnosis of Barrett's esophagus in a given patient from a particular study cannot necessarily be construed as the absence of a prior diagnosis of Barrett's esophagus. Although underreporting is thus possible, it seems unlikely for the reasons previously enumerated.

All but one³⁷ of the included studies reflected the experience of a single referral center population. Observational studies from referral centers may be subject to selection bias. Patients with potentially curable adenocarcinoma, especially those with Barrett's associated dysplasia detected during surveillance, may be more likely to be referred to and followed by physicians practicing in referral centers. In contrast, patients presenting with incurable cancer may be more likely to be managed locally by their community healthcare provider. Furthermore, routine endoscopic screening and surveillance of Barrett's esophagus is more likely to occur in referral centers. It thus seems that selection bias, if present, would tend to overestimate the proportion of patients undergoing surgical resection with a prior diagnosis of Barrett's. In support of this view, the single population-based study identified in this review reported that only 2% of cases undergoing resection had a prior diagnosis of Barrett's esophagus.³⁷ Moreover, this population-based study suggested that <1% of all incident cases of adenocarcinoma (i.e., those undergoing resection as well as those who did not) had a prior diagnosis of Barrett's esophagus.

Preliminary reports from more recent population-based studies seem to be consistent with the findings of the present study. One study used SEER tumor registries to identify a cohort of 1633 cases of esophageal/cardia

adenocarcinoma from 1993 to 1996 in patients at least 70 years of age. These cases were linked to Medicare files to identify those 158 of 1633 (10%) who had filed a claim for upper endoscopy from 1991 up to 1 year before the diagnosis of adenocarcinoma.⁵³ A second preliminary report examined medical records of 589 incident esophageal/cardia adenocarcinoma cases in the Northern California Kaiser Permanente population from 1990–1998 and showed that although Barrett's esophagus was found in 135 of 589 (23%), only 64 of 589 (11%) had undergone endoscopy at least 6 months before the diagnosis of cancer, and only 23 of 589 (4%) cases had a diagnosis of Barrett's made at least 6 months before the diagnosis of adenocarcinoma.⁵⁴

The studies included in this review do not constitute a representative, probabilistic sample of those with esophageal adenocarcinoma. Therefore, given the possibility of heterogeneity across the 12 studies included in this review, as well as the strong possibility of sampling bias, any pooled, summary estimate of the proportion of all patients undergoing resection who had a prior diagnosis of Barrett's esophagus should be interpreted with some caution. With these caveats, the random effects model estimate of $4.7\% \pm 2.9\%$ may be the most appropriate, given the available data.

In summary, a very small proportion (~5%) of patients reported to have undergone resection of esophageal adenocarcinoma were known to have a prior diagnosis of Barrett's esophagus and were thus eligible for surveillance. The low prior prevalence of Barrett's esophagus in this study population provides indirect evidence to suggest that recent efforts to identify patients with Barrett's—whether through endoscopic screening or evaluation of symptomatic patients—have had minimal public health impact on esophageal adenocarcinoma outcomes. The potential benefits of endoscopic surveillance have thus been limited to only a fraction of those individuals at risk. These data provide a compelling rationale for the development, evaluation, and implementation of effective screening strategies to identify patients with Barrett's esophagus. Such screening programs should be paired with surveillance programs that have been subject to similarly rigorous evaluation. Prospective studies of screening and surveillance will require collaboration and a substantial investment of resources, but such studies are the necessary first steps to decreasing morbidity and mortality from Barrett's associated cancer in the population.

References

1. Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. *Hum Pathol* 1994;25:982–993.

2. Cameron AJ, Ott BJ, Payne WS. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. *N Engl J Med* 1985;313:857-859.
3. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. *Semin Oncol* 1999;26:2-8.
4. National Cancer Institute. SEER Cancer Statistics Review, 1973-1997: Table VIII-4. p. 185. Surveillance Epidemiology and End Results Website. Accessed May 1, 2000. http://seer.cancer.gov/Publications/CSR1973_1997.
5. Reis I, Kosary C, Hankey B, Fever E, Merrill R, Clagg L. Cancer Statistics Review 1993-1994. NIH Publication No. 97-2789. U.S. Department of Health and Human Services, Bethesda, MD, 1997.
6. Pera M. Epidemiology of esophageal cancer, especially adenocarcinoma of the esophagus and esophagogastric junction. *Recent Results Cancer Res* 2000;155:1-14.
7. Mueller J, Werner M, Siewert JR. Malignant progression in Barrett's esophagus: pathology and molecular biology. *Recent Results Cancer Res* 2000;155:29-41.
8. Ruol A, Parenti A, Zaninotto G, Merigliano S, Costantini M, Cagol M, Alfieri R, Bonavina L, Peracchia A, Ancona E. Intestinal metaplasia is the probable common precursor of adenocarcinoma in Barrett esophagus and adenocarcinoma of the gastric cardia. *Cancer* 2000;88:2520-2528.
9. Clark GW, Smyrk TC, Burdiles P, Hoeft SF, Peters JH, Kiyabu M, Hinder RA, Bremner CG, DeMeester TR. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? *Arch Surg* 1994;129:609-614.
10. 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;93:1028-1032.
11. Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings [see comments]. *Gastroenterology* 1990;99:918-922.
12. Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. 2nd ed. Oxford University Press, New York, NY, 2000.
13. Kuster GG, Foroozan P. Early diagnosis of adenocarcinoma developing in Barrett's esophagus. *Arch Surg* 1989;124:925-927.
14. Ellis FH Jr. Treatment of carcinoma of the esophagus or cardia. *Mayo Clin Proc* 1989;64:945-955.
15. MacDonald WC, MacDonald JB. Adenocarcinoma of the esophagus and/or gastric cardia. *Cancer* 1987;60:1094-1098.
16. Steiger Z, Wilson RF, Leichman L, Busuito MJ, Rosenberg JC. Primary adenocarcinoma of the esophagus. *J Surg Oncol* 1987;36:68-70.
17. Mitchell RL. Abdominal and right thoracotomy approach as standard procedure for esophagogastrectomy with low morbidity. *J Thorac Cardiovasc Surg* 1987;93:205-211.
18. Rogers EL, Goldkind SF, Iseri OA, Bustin M, Goldkind L, Hamilton SR, Smith RL. Adenocarcinoma of the lower esophagus. A disease primarily of white men with Barrett's esophagus. *J Clin Gastroenterol* 1986;8:613-618.
19. Yoshida M, Ide H, Yamada A, Endo M. Early detection of adenocarcinoma of the esophagus. *Endoscopy* 1986;18(suppl 3):44-48.
20. Wang HH, Antonioli DA, Goldman H. Comparative features of esophageal and gastric adenocarcinomas: recent change in type and frequency. *Hum Pathol* 1986;17:482-487.
21. Peters JH, Clark GW, Ireland AP, Chandrasoma P, Smyrk TC, DeMeester TR. Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients. *J Thorac Cardiovasc Surg* 1994;108:813-821.
22. Lerut T, Coosemans W, Van Raemdonck D, Dillemans B, De Leyn P, Marnette JM, Geboes K. Surgical treatment of Barrett's carcinoma. Correlations between morphologic findings and prognosis. *J Thorac Cardiovasc Surg* 1994;107:1059-1065.
23. Wolfe WG, Vaughn AL, Seigler HF, Hathorn JW, Leopold KA, Duhaylongsod FG. Survival of patients with carcinoma of the esophagus treated with combined-modality therapy. *J Thorac Cardiovasc Surg* 1993;105:749-755.
24. Streitz JM Jr., Andrews CW Jr., Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? *J Thorac Cardiovasc Surg* 1993;105:383-387.
25. Moghissi K, Sharpe DA, Pender D. Adenocarcinoma and Barrett's oesophagus. A clinico-pathological study. *Eur J Cardiothorac Surg* 1993;7:126-131.
26. Menke-Pluymers MB, Schoute NW, Mulder AH, Hop WC, van Blankenstein M, Tilanus HW. Outcome of surgical treatment of adenocarcinoma in Barrett's oesophagus. *Gut* 1992;33:1454-1458.
27. Gray JR, Coldman AJ, MacDonald WC. Cigarette and alcohol use in patients with adenocarcinoma of the gastric cardia or lower esophagus. *Cancer* 1992;69:2227-2231.
28. Harvey JC, Kagan AR, Hause D, Sachs T, Frankl H. Adenocarcinoma arising in Barrett's esophagus. *J Surg Oncol* 1990;45:162-163.
29. Hoff SJ, Sawyers JL, Blanke CD, Choy H, Stewart JR. Prognosis of adenocarcinoma arising in Barrett's esophagus. *Ann Thorac Surg* 1998;65:176-180.
30. Chalasani N, Wo JM, Waring JP. Racial differences in the histology, location, and risk factors of esophageal cancer. *J Clin Gastroenterol* 1998;26:11-13.
31. Collard JM, Romagnoli R, Hermans BP, Malaise J. Radical esophageal resection for adenocarcinoma arising in Barrett's esophagus. *Am J Surg* 1997;174:307-311.
32. Ruol A, Merigliano S, Baldan N, Santi S, Petrin GF, Bonavina L, Ancona E, Peracchia A. Prevalence, management and outcome of early adenocarcinoma (pT1) of the esophago-gastric junction. Comparison between early cancer in Barrett's esophagus (type I) and early cancer of the cardia (type II). *Dis Esophagus* 1997;10:190-195.
33. Agha FP. Barrett carcinoma of the esophagus: clinical and radiographic analysis of 34 cases. *AJR Am J Roentgenol* 1985;145:41-46.
34. Levine MS, Caroline D, Thompson JJ, Kressel HY, Laufer I, Herlinger H. Adenocarcinoma of the esophagus: relationship to Barrett mucosa. *Radiology* 1984;150:305-309.
35. Saubier EC, Gouillat C, Samaniego C, Guillaud M, Moulinier B. Adenocarcinoma in columnar-lined Barrett's esophagus. Analysis of 13 esophagectomies. *Am J Surg* 1985;150:365-369.
36. Harle IA, Finley RJ, Belsheim M, Bondy DC, Booth M, Lloyd D, McDonald JW, Sullivan S, Valberg LS, Watson WC, Frei JV, Slinger R, Troster M, Meads GE, Duff JH. Management of adenocarcinoma in a columnar-lined esophagus. *Ann Thorac Surg* 1985;40:330-336.
37. Bytzer P, Christensen PB, Damkier P, Vinding K, Seersholm N. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. *Am J Gastroenterol* 1999;94:86-91.
38. Peracchia A, Bonavina L, Via A, Incarbone R. Current trends in the surgical treatment of esophageal and cardia adenocarcinoma. *J Exp Clin Cancer Res* 1999;18:289-294.
39. van Sandick JW, van Lanschot JJ, Kuiken BW, Tytgat GN, Offerhaus GJ, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. *Gut* 1998;43:216-222.
40. Holscher AH, Bollschweiler E, Schneider PM, Siewert JR. Early adenocarcinoma in Barrett's oesophagus. *Br J Surg* 1997;84:1470-1473.
41. Thomas P, Doddoli C, Lienne P, Morati N, Thirion X, Garbe L, Guidicelli R, Fuentes P. Changing patterns and surgical results in

- adenocarcinoma of the oesophagus. *Br J Surg* 1997;84:119–125.
42. Johansson J, Johnsson F, Walther B, Willen R, Stael vH, Zilling T. Adenocarcinoma in the distal esophagus with and without Barrett esophagus. Differences in symptoms and survival rates. *Arch Surg* 1996;131:708–713.
 43. Cameron AJ, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. *Gastroenterology* 1995;109:1541–1546.
 44. Li H, Walsh TN, Hennessy TP. Carcinoma arising in Barrett's esophagus. *Surg Gynecol Obstet* 1992;175:167–172.
 45. Moon MR, Schulte WJ, Haasler GB, Condon RE. Transhiatal and transthoracic esophagectomy for adenocarcinoma of the esophagus. *Arch Surg* 1992;127:951–955.
 46. Ribet ME, Mensier EA. Reflux esophagitis and carcinoma. *Surg Gynecol Obstet* 1992;175:121–125.
 47. Duhaylongsod FG, Wolfe WG. Barrett's esophagus and adenocarcinoma of the esophagus and gastroesophageal junction. *J Thorac Cardiovasc Surg* 1991;102:36–41.
 48. Hamilton SR, Smith RR, Cameron JL. Prevalence and characteristics of Barrett esophagus in patients with adenocarcinoma of the esophagus or esophagogastric junction. *Hum Pathol* 1988;19:942–948.
 49. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340:825–831.
 50. Falk GW, Rice TW, Goldblum JR, Richter JE. Jumbo biopsy forceps protocol still misses unsuspected cancer in Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc* 1999;49:170–176.
 51. Pera M. Epidemiology of esophageal cancer, especially adenocarcinoma of the esophagus and esophagogastric junction. *Recent Results Cancer Res* 2000;155:1–14.
 52. Hansen S, Melby KK, Aase S, Jellum E, Vollset SE. *Helicobacter pylori* infection and risk of cardia cancer and non-cardia gastric cancer—a nested case-control study. *Scand J Gastroenterol* 1999;34:353–360.
 53. Cooper GS, Yuan Z, Chak A, Rimm AA. Pre-diagnosis endoscopy is associated with improved staging and survival for adenocarcinoma of the esophagus and cardia (abstr). *Gastrointest Endosc* 2001;53:AB152.
 54. Corley D, Levin TR, Buffler P. Association between surveillance and survival in Barrett's adenocarcinoma: a population-based study (abstr). *Gastroenterology* 2001;120(suppl 1):A-17.
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