Are we making progress in preventing Barrett's-related esophageal cancer?

Julian A. Abrams

Therapeutic Advances in Gastroenterology

[2009] 2(2) 73–77

DOI: 10.1177/
1756283X08102044

© The Author(s), 2009.

Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Introduction

Over the past three decades, the incidence of both Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) has risen at an alarming rate. The prevalence of Barrett's esophagus in Western countries is currently estimated at 1–5%, and its presence is associated with a 25- to 30-fold increased risk of esophageal adenocarcinoma [Ronkainen *et al.* 2005; Conio *et al.* 2001; Cameron *et al.* 1990]. The incidence of EAC has increased more than five-fold in the United States in the past three decades [Brown *et al.* 2008], and recent data from the United Kingdom demonstrate a similar epidemic rise [Lepage *et al.* 2008]. Increased awareness of and diagnosis of Barrett's esophagus has resulted in greater surveillance for BE. This could, in theory, result in diagnosis of a greater number of cases of early-stage esophageal cancer and an apparent increased incidence in EAC due to lead time bias. However, the overall rise in incidence is not merely an artefact of endoscopic surveillance in BE. Surveillance, Epidemiology, and End Results (SEER) data demonstrate that the incidence curves over the past 30 years are nearly identical for localized, regional and distant disease [Brown *et al.* 2008]. The rise in incidence is all the more alarming given the dismal prognosis for patients with EAC, which is still associated with an overall 5-year survival of only 16% [Jemal *et al.* 2008]. While the reasons for these disturbing trends are not entirely clear, there is no doubt that improvements are needed with respect to esophageal adenocarcinoma prevention.

Endoscopic surveillance for Barrett's esophagus

At present, endoscopic surveillance for patients with BE is the only means widely employed in the attempt to improve overall outcomes in EAC. There are several problems with a 'prevention' strategy that relies solely on endoscopic surveillance. Firstly, BE must be identified prior to the development of EAC. In a population-based study by Corley *et al.* [2002], only 5% of EAC patients had been diagnosed with BE at least 6 months prior to their cancer diagnosis. The prevalence of frequent gastro-esophageal reflux disease (GERD) symptoms in the United States is estimated at 20–25% [El-Serag *et al.* 2004b], but BE is present only in a small fraction. Additionally, a high proportion of patients with BE deny any prior GERD-like symptoms [Rex *et al.* 2003]. Therefore, performing screening endoscopy on everyone with GERD would not be the most effective or cost-efficient strategy to identify BE patients.

The majority of patients diagnosed with BE undergo endoscopic surveillance. The goal of surveillance is to detect high-grade dysplasia (HGD) or early-stage EAC, thereby 'stage shifting' to increase the proportion with early-stage disease and hopefully improving overall outcomes. There are two key elements of endoscopic surveillance for BE. The first is to perform examinations at appropriate intervals, as outlined in the updated American College of Gastroenterology (ACG) guidelines [Wang and Sampliner, 2008]. Prior studies have demonstrated high compliance

Correspondence to:

Julian A. Abrams, MD, MS
Department of Medicine,
Columbia University
College of Physicians and
Surgeons, New York, USA;
and Herbert Irving
Comprehensive Cancer
Center, Columbia
University, New York, USA
ja660@columbia.edu

(84–98%) among practicing gastroenterologists with regard to adherence to recommended surveillance intervals [Falk *et al.* 2000; van Sandick *et al.* 2000]. The second element of the BE surveillance endoscopy consists of adequate biopsy sampling in order to detect any dysplasia or carcinoma, as dysplastic tissue can be present within endoscopically normal-appearing BE. Since 1998, the ACG has recommended four quadrant random biopsies every 2 cm throughout the BE segment [Sampliner, 1998]. However, adherence to this guideline in the community is substantially lower than observed for surveillance intervals. Anonymous surveys in the United States and Europe have found adherence to this recommended sampling technique among 42–77% of gastroenterologists [Das *et al.* 2008; Amamra *et al.* 2007; Mandal *et al.* 2003; Ofman *et al.* 2001; Falk *et al.* 2000; van Sandick *et al.* 2000]. In a recent study of a national community-based pathology database, adherence to biopsy recommendations was observed in only 51% of cases of established Barrett's esophagus. More importantly, nonadherence to the guidelines was associated with a significantly lower detection of dysplasia (adjusted OR 0.53, 95% CI 0.35–0.82) [Abrams *et al.* 2009].

Effective endoscopic surveillance also relies on histologic diagnoses from biopsies in order to appropriately risk stratify patients with regard to progression to cancer, thus determining subsequent surveillance intervals as well as the potential need for treatment. Unfortunately, the diagnosis of dysplasia is not a straightforward matter. Inflammation due to acid reflux can result in reactive atypia, changes that appear very similar to those of low-grade dysplasia. A study by Montgomery *et al.* [2001] demonstrated poor inter- and intraobserver agreement among pathologists for the determination of low-grade dysplasia. Therefore, ACG guidelines recommend that any diagnosis of low-grade dysplasia or greater be confirmed by a second 'expert' gastrointestinal pathologist.

The overwhelming majority of nondysplastic BE patients will never develop EAC [Conio *et al.* 2003; Drewitz *et al.* 1997]. As a result, a large number of endoscopies are performed on patients who will never develop disease. Several candidate biomarkers, such as p16, p53, aneuploidy, and cyclin D1, have been identified in an attempt to better risk stratify patients for

progression [Badreddine and Wang, 2008]. However, none of these has been prospectively validated, either alone or in combination with histology, as predictors of neoplastic progression.

Endoscopic therapy

Surveillance in and of itself does not necessarily prevent EAC, but rather allows for the timely identification of patients who have progressed to high-grade dysplasia or early EAC. Endoscopic ablation, including photodynamic therapy, radiofrequency ablation and cryotherapy with liquid nitrogen, are all methods that can successfully destroy dysplastic BE and result in regrowth of normal-appearing neosquamous epithelium. In a randomized controlled trial of photodynamic therapy (PDT) for the treatment of BE with HGD, PDT was 77% effective at eliminating HGD [Overholt *et al.* 2005], with 6.2% of patients developing esophageal cancer during the follow-up period [Prasad *et al.* 2007]. A more recent randomized sham-controlled trial of radiofrequency ablation reported that treatment completely eradicated dysplasia HGD in 80% of cases at one year (data presented at 2008 Digestive Disease Week) [Shaheen *et al.* 2008]. Whether the strategy of endoscopic surveillance combined with endoscopic treatment for HGD will actually reduce the incidence of EAC is not known.

As a result of the promising data in patients with HGD, the question arises as to whether ablation should be performed on patients with low-grade or no dysplasia for the prevention of EAC. Successful elimination of Barrett's metaplasia using radiofrequency ablation was achieved in 97% of patients at 2.5 years of follow-up [Fleischer *et al.* 2008]. However, there is no data available with regard to cancer incidence postablation in this group of patients. There are several reasons to argue against the use of ablation for nondysplastic BE. While the relative risk of EAC in BE patients is much higher than in the general population, the absolute risk is still very low. Therefore, the number needed to treat (NNT) to prevent a single cancer is very high, necessitating that any intervention in nondysplastic patients be both extremely effective and safe. Given currently available data, the number of complications due to ablative procedures would far exceed the number of cancers prevented.

Secondly, long-term data is not available to justify ceasing endoscopic surveillance after endoscopic ablation. This results in limitation of the cost-effectiveness of this strategy, as patients are still obligated to undergo periodic postablation endoscopies. Thirdly, data from PDT ablation for HGD demonstrated that nonresponders to ablation were more likely to have pretreatment allelic loss of p16 [Prasad *et al.* 2008], and altered p16 expression has been observed in association with EAC. The implication of this finding is that ablation may be less effective at preventing cancer than would be suggested by the clinical trials. If nonresponders are the patients at baseline most likely to develop EAC, then ablation would be most effective for the patients who are least likely to develop cancer in the first place, obviously limiting the efficacy of ablation as a strategy to prevent EAC.

Chemoprevention

Is there effective chemoprevention for neoplastic progression in Barrett's esophagus? While the vast majority of patients with BE are prescribed proton pump inhibitors (PPIs), there is little concrete evidence to demonstrate that acid suppression prevents the development of dysplasia and cancer. Epidemiologic studies have had inconsistent findings with regard to PPI use and risk of EAC [Garcia Rodriguez *et al.* 2006; El-Serag *et al.* 2004a], and published laboratory data are even less clear with regard to the role of acid in the development of BE-associated neoplasia. Multiple large cohort studies have found that the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a decreased odds of EAC [Vaughan *et al.* 2005; Corley *et al.* 2003]. The Aspirin for the Prevention of Esophageal Cancer Trial (AsPECT) is an ongoing randomized clinical trial with a 2 × 2 study design, in which nondysplastic BE patients are assigned to either 20 mg or 80 mg of esomeprazole and either aspirin 300 mg or no aspirin [Jankowski and Moayyedi, 2004]. The primary outcome of the study is the development of HGD or EAC. This study will hopefully shed light on the role of aspirin as a chemopreventive agent as well as whether increased acid suppression with higher dose PPIs is more or less effective at cancer prevention.

Various epidemiologic studies suggest that consumption of high levels of folic acid, green tea, berries, and antioxidants may all be associated with reduced odds of EAC. However, there is currently no clinical trial data to support their use as chemopreventive agents in patients with BE.

Summary

Despite the increased awareness and recognition of Barrett's esophagus, the incidence of EAC continues to rise sharply in the Western world. Attempts to improve outcomes for this deadly disease rely on the detection of BE; unfortunately, the majority of EAC patients never receive a prior diagnosis of BE. Additionally, endoscopic surveillance has limitations. Studies have demonstrated suboptimal biopsy sampling among practicing gastroenterologists, and the determination of dysplasia, the basis of risk stratification in BE, is associated with relatively low interobserver agreement. Candidate biomarkers are under investigation for the identification of patients at highest risk for neoplastic progression, although these have not yet been prospectively validated. Endoscopic therapies are effective for the treatment of high-grade dysplasia and intramucosal carcinoma. However, the use of these techniques for BE patients without dysplasia cannot currently be recommended for the prevention of EAC. There are no current chemopreventive agents that can be advocated for use in all BE patients. Hopefully, the AsPECT study will shed light on the roles of both PPIs and aspirin for the prevention of EAC. It is hoped that current and future research will ultimately provide enough answers to help slow the epidemic rise in incidence of esophageal adenocarcinoma.

Conflict of interest statement

None declared.

References

- Abrams, J.A., Kapel, R.C., Lindberg, G.M., Saboorian, M.H., Genta, R.M., Neugut, A.I. *et al.* (2009) Adherence to biopsy guidelines for Barrett's esophagus surveillance in the community setting in the United States, *Clin Gastroenterol Hepatol* (in press).
- Amamra, N., Touzet, S., Colin, C. and Ponchon, T. (2007) Current practice compared with the international guidelines: endoscopic surveillance of Barrett's esophagus, *J Eval Clin Pract* 13: 789–794.

- Badreddine, R. and Wang, K.K. (2008) Biomarkers in gastrointestinal cancers, *Am J Gastroenterol* 103: 2106–2610.
- Brown, L.M., Devesa, S.S. and Chow, W.H. (2008) Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age, *J Natl Cancer Inst* 100: 1184–1187.
- Cameron, A.J., Zinsmeister, A.R., Ballard, D.J. and Carney, J.A. (1990) Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings, *Gastroenterology* 99: 918–922.
- Conio, M., Bianchi, S., Lapertosa, G., Ferraris, R., Sablich, R., Marchi, S. *et al.* (2003) Long-term endoscopic surveillance of patients with Barrett's esophagus. Incidence of dysplasia and adenocarcinoma: a prospective study, *Am J Gastroenterol* 98: 1931–1939.
- Conio, M., Cameron, A.J., Romero, Y., Branch, C.D., Schleck, C.D., Burgart, L.J. *et al.* (2001) Secular trends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota, *Gut* 48: 304–309.
- Corley, D.A., Kerlikowske, K., Verma, R. and Buffler, P. (2003) Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis, *Gastroenterology* 124: 47–56.
- Corley, D.A., Levin, T.R., Habel, L.A., Weiss, N.S. and Buffler, P.A. (2002) Surveillance and survival in Barrett's adenocarcinomas: a population-based study, *Gastroenterology* 122: 633–640.
- Das, D., Ishaq, S., Harrison, R., Kosuri, K., Harper, E., Decaestecker, J. *et al.* (2008) Management of Barrett's esophagus in the UK: Overtreated and underbiopsied but improved by the introduction of a national randomized trial, *Am J Gastroenterol* 103: 1079–89.
- Drewitz, D.J., Sampliner, R.E. and Garewal, H.S. (1997) The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years, *Am J Gastroenterol* 92: 212–215.
- El-Serag, H.B., Aguirre, T.V., Davis, S., Kuebel, M., Bhattacharyya, A. and Sampliner, R.E. (2004a) Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus, *Am J Gastroenterol* 99: 1877–1883.
- El-Serag, H.B., Petersen, N.J., Carter, J., Graham, D.Y., Richardson, P., Genta, R.M. *et al.* (2004b) Gastroesophageal reflux among different racial groups in the United States, *Gastroenterology* 126: 1692–1699.
- Falk, G.W., Ours, T.M. and Richter, J.E. (2000) Practice patterns for surveillance of Barrett's esophagus in the united states, *Gastrointest Endosc* 52: 197–203.
- Fleischer, D.E., Overholt, B.F., Sharma, V.K., Reymunde, A., Kimmey, M.B., Chuttani, R. *et al.* (2008) Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up, *Gastrointest Endosc* 68: 867–876.
- Garcia Rodriguez, L.A., Lagergren, J. and Lindblad, M. (2006) Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK, *Gut* 55: 1538–1544.
- Jankowski, J. and Moayyedi, P. (2004) Re: Cost-effectiveness of aspirin chemoprevention for Barrett's esophagus, *J Natl Cancer Inst* 96: 885–887; author reply 887.
- Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T. *et al.* (2008) Cancer statistics, 2008, *CA Cancer J Clin* 58: 71–96.
- Lepage, C., Rachet, B., Jooste, V., Faivre, J. and Coleman, M.P. (2008) Continuing rapid increase in esophageal adenocarcinoma in England and Wales, *Am J Gastroenterol* 103: 2694–2699.
- Mandal, A., Playford, R.J. and Wicks, A.C. (2003) Current practice in surveillance strategy for patients with Barrett's oesophagus in the UK, *Aliment Pharmacol Ther* 17: 1319–1324.
- Montgomery, E., Bronner, M.P., Goldblum, J.R., Greenson, J.K., Haber, M.M., Hart, J. *et al.* (2001) Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation, *Hum Pathol* 32: 368–378.
- Ofman, J.J., Shaheen, N.J., Desai, A.A., Moody, B., Bozyski, E.M. and Weinstein, W.M. (2001) The quality of care in Barrett's esophagus: endoscopist and pathologist practices, *Am J Gastroenterol* 96: 876–881.
- Overholt, B.F., Lightdale, C.J., Wang, K.K., Canto, M.I., Burdick, S., Haggitt, R.C. *et al.* (2005) Photodynamic therapy with porfimer sodium for ablation of high-grade dysplasia in Barrett's esophagus: international, partially blinded, randomized phase III trial, *Gastrointest Endosc* 62: 488–498.
- Prasad, G.A., Wang, K.K., Buttar, N.S., Wongkeesong, L.M., Krishnadath, K.K., Nichols 3rd F.C. *et al.* (2007) Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus, *Gastroenterology* 132: 1226–1233.
- Prasad, G.A., Wang, K.K., Halling, K.C., Buttar, N.S., Wongkeesong, L.M., Zinsmeister, A.R. *et al.* (2008) Utility of biomarkers in prediction of response to ablative therapy in Barrett's esophagus, *Gastroenterology* 135: 370–379.
- Rex, D.K., Cummings, O.W., Shaw, M., Cumings, M.D., Wong, R.K., Vasudeva, R.S. *et al.* (2003) Screening for Barrett's esophagus in

colonoscopy patients with and without heartburn, *Gastroenterology* 125: 1670–1677.

Ronkainen, J., Aro, P., Storskrubb, T., Johansson, S.E., Lind, T., Bolling-Sternevald, E. *et al.* (2005) Prevalence of Barrett's esophagus in the general population: an endoscopic study, *Gastroenterology* 129: 1825–1831.

Sampliner, R.E. (1998) 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* 93: 1028–1032.

Shaheen, N.J., Sharma, P., Overholt, B.F., Lightdale, C.J., Wolfsen, H.C., Sampliner, R.E. *et al.* (2008) A randomized, multicenter, sham-controlled trial of radiofrequency ablation (RFA) for Subjects with Barrett's esophagus (BE) containing

dysplasia: Interim results of the AIM Dysplasia Trial, *Gastroenterology* 134: A37.

van Sandick, J.W., Bartelsman, J.F., van Lanschot, J.J., Tytgat, G.N. and Obertop, H. (2000) Surveillance of Barrett's oesophagus: physicians' practices and review of current guidelines, *Eur J Gastroenterol Hepatol* 12: 111–117.

Vaughan, T.L., Dong, L.M., Blount, P.L., Ayub, K., Odze, R.D., Sanchez, C.A. *et al.* (2005) Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study, *Lancet Oncol* 6: 945–952.

Wang, K.K. and Sampliner, R.E. (2008) Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus, *Am J Gastroenterol* 103: 788–797.

Visit SAGE journals online
<http://tag.sagepub.com>

SAGE JOURNALS
Online