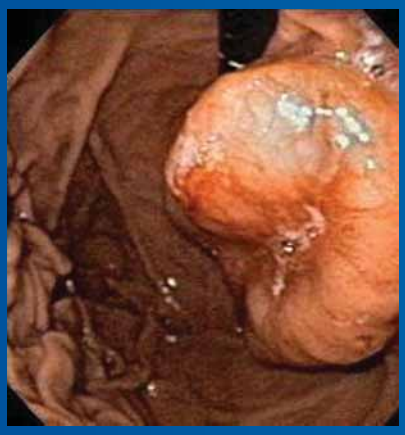
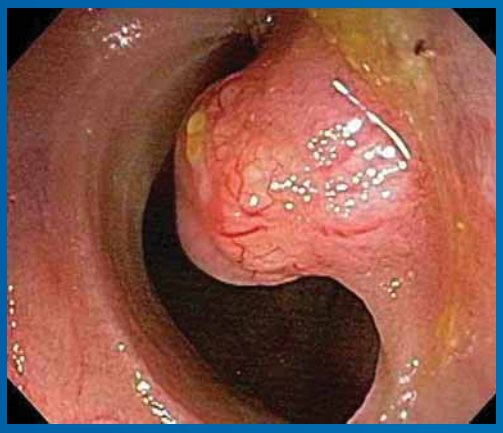
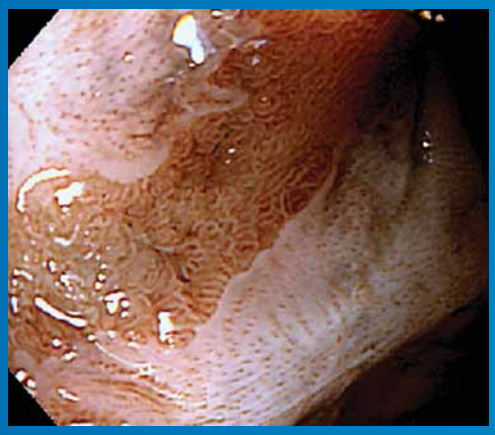
Endoscopic Oncology

Gastrointestinal Endoscopy and Cancer Management

Edited by

DOUGLAS O. FAIGEL, MD, FACG, FASGE

MICHAEL L. KOCHMAN, MD, FACP, FASGE

HUMANA PRESS

Endoscopic Oncology

Endoscopic Oncology

Gastrointestinal Endoscopy and Cancer Management

Edited by

Douglas O. Faigel, MD, FACG, FASGE

Associate Professor of Medicine, Director of Endoscopy
Oregon Health and Science University, Portland, OR

Michael L. Kochman, MD, FACP, FASGE

Professor of Medicine and Surgery, Co-Director Gastrointestinal Oncology,
Hospital of the University of Pennsylvania, Philadelphia, PA

Humana Press
Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel: 973-256-1699; Fax: 973-256-8341; E-mail: orders@humanapr.com or visit our website at www.humanapress.com

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute)
Permanence of Paper for Printed Library Materials.

Production Editor: Melissa Caravella

Cover design by Patricia F. Cleary

Cover illustration: From Fig. 5B in Chapter 3, "Image Enhancement Endoscopy," by Stephan M. Wildi and Michael B. Wallace;Fig. 2 in Chapter 13, "Diagnosis and Management of Gastrointestinal Lymphoma," by John G. Kuldau, Peter R. Holman, and Thomas J. Savides; and Fig. 1A in Chapter 15, "Carcinoid Tumors," by Willscott E. Naugler and Gordon C. Hunt.

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59745-172-X

Library of Congress Cataloging-in-Publication Data

Endoscopic oncology : gastrointestinal endoscopy and cancer management / edited by Douglas O. Faigel, Michael L. Kochman.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-58829-532-X (alk. paper)
1. Endoscopy. 2. Gastrointestinal system--Cancer--Endoscopic surgery. 3. Gastrointestinal system--Diseases--Diagnosis.
[DNLM: 1. Neoplasms--therapy. 2. Endoscopy, Gastrointestinal--methods. QZ 268 E556 2006] I. Faigel, Douglas O. II. Kochman, Michael L.
RC804.E6E53 2006
616.99'407545--dc22
2005036564

Preface

Cancer is the second most common cause of death in Americans (*see* www.cdc.gov). Colorectal cancer kills more Americans than any other malignancy except for lung cancer. The incidences and mortalities of the major gastrointestinal (GI) malignancies are shown in Table 1. Taken as a group, the five most common GI malignancies account for more cancers and more cancer deaths than for any other site.

Flexible endoscopy has given physicians unprecedented access to the GI tract. The ability to endoscopically visualize, biopsy, and apply therapy has had implications for the management of all the major GI malignancies. Accepted applications of endoscopy range from detection of malignant and premalignant lesions (e.g., colonoscopy for colon cancer screening), prevention of cancers through removal of precursor lesions (e.g., polypectomy), surveillance of premalignant conditions (e.g., Barrett's esophagus), palliation of symptoms (e.g., placement of stents for biliary or esophageal obstruction) or staging of cancers to allow stage directed therapy (e.g., endoscopic ultrasound), and, in selected circumstances, definitive therapy for early stage neoplasms (e.g., endoscopic mucosal resection). This partial list of applications demonstrates the central role that endoscopy plays in management for those at risk for or with a GI malignancy. The wide variety of endoscopic techniques applied suggests a new subspecialty of endoscopy: "endoscopic oncology." This is similar to "surgical oncology," as it concerns itself with the subset of endoscopic procedures directly applied for the management of neoplastic and precancerous conditions.

It becomes apparent that a substantial proportion of endoscopies are performed for a cancer-related indication. To determine what proportion of endoscopic procedures are done out of a concern for cancer or a premalignant condition, a large national database of endoscopic reports (Clinical Outcomes Research Initiative [CORI]) was queried. Indications related to cancer were defined by convening an expert panel (Table 2).* We then queried the CORI database to determine the proportion of endoscopies done for these indications. The CORI database encompassed 105 practice sites in 28 states and had data on 245,971 patients.

The results demonstrated that the majority of endoscopic procedures (63.5%) in these practices were performed owing to a primary concern for cancer (Fig. 1). In fact, only for EGD were the majority not done for a cancer-related indication (32.7%). The great majority of colonoscopy (84.4%), ERCP (59.9%), and EUS (98.7%) procedures are done for cancer-related indications. For colonoscopy, the major cancer-related indications are surveillance of patients with prior polyps (21.3% of cancer-related indications), evaluation of hematochezia (26.2%), follow-up of a positive hemoccult test (15.6%), or surveillance in a patient with a family history of colorectal cancer (17.8%). For EGD, dysphagia was the most common cancer-related indication (62.4%) followed by anemia (23%) and Barrett's screening/surveillance (12.2%). For ERCP, 98% of the cancer-related indications are related to bile duct obstruction. For EUS, the primary indications related to cancer are FNA of a mass (26%), stage a known cancer (23%), or evaluate a pancreas lesion (23%).

Table 1
Incidence and Mortality of the Five Most Common Gastrointestinal Malignancies

Site	*Incidence*[a]	*Mortality*[a]
Colorectum	53.9	21.6
Pancreas	11.1	10.6
Stomach	9.1	4.9
Liver/intrahepatic bile ducts	6.2	4.4
Esophagus	4.5	4.3

Data from SEER database 1992–2002 (www.seer.cancer.gov).
[a]Per 100,000.

Table 2
Cancer-Related Indications for Endoscopic Procedures

EGD	Dysphagia, Barrett's, anemia, f/u gastric ulcer, familial polyposis, abnormal X-ray
Colonoscopy	Heme+, CRC screen/surveillance, ulcerative colitis screening, polyp on flex sig, family history, hematochezia, f/u polyp abnormal X-ray
ERCP	Jaundice, biliary obstruction, stricture, pancreatic duct obstruction, stent placement, abnormal X-ray
EUS	Cancer staging, fine needle aspiration, submucosal tumor, stricture, pancreatic mass/cyst, lymphadenopathy, abnormal X-ray

*Faigel DO, Lieberman DA, Falk GW, et al. Endoscopic oncology: cancr as an indication for gastrointestinal endoscopy in the United States. Gastrointest Endosc 2002; 55(5):AB164.

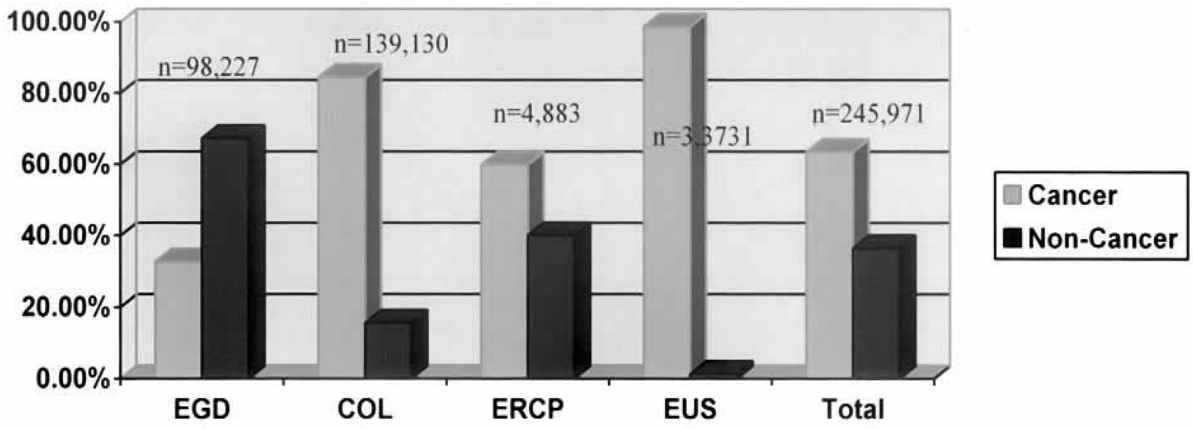


Fig. 1. Proportion of endoscopic procedures done for cancer-related indications. (Data from the CORI database.)

With nearly two-thirds of all endoscopic procedures being done out of a primary concern for cancer, it is apparent that all of us who do endoscopy are endoscopic oncologists!

This textbook examines the interface between endoscopy and oncology. It is organized anatomically: esophagus, stomach, colorectum, and pancreaticobiliary. For each site, the relevant cancers and premalignant conditions are addressed and the use of endoscopy in their diagnosis, management, and treatment discussed in detail. Additionally, the reader will find chapters summarizing the state-of-the-art for nonendoscopic medical and surgical cancer treatment.

This book was written with the practicing endoscopist in mind. However, given the multidisciplinary approach of modern cancer care, this book will be of interest to all health care professionals who take care of cancer patients, including medical oncologists, radiation oncologists, and surgeons.

Douglas O. Faigel, *MD, FACG*
Michael L. Kochman, *MD, FACP*

Contents

Contributors

Nuzhat A. Ahmad, MD, *Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA*

Kevin G. Billingsley, MD, *Department of Surgery, Oregon Health and Science University, Portland, OR*

Charles D. Blanke, MD, *Division of Hematology and Oncology, Oregon Health and Science University, Portland, OR*

William R. Brugge, MD, *Department of Medicine, Massachusetts General Hospital, Boston, MA*

Christopher A. Canning, MD, *Department of Radiation Oncology, Oregon Health and Science University, Portland, OR*

Marcia I. Canto, MD, MHS, *Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, MD*

Amitabh Chak, MD, *Division of Gastroenterology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH*

Yang K. Chen, MD, *Professor of Medicine, Gastrointestinal Practice Director/Director of Endoscopy, University of Colorado Hospital, Anschutz Outpatient Pavilion Aurora, CO*

Raquel E. Davila, MD, *Division of Gastroenterology, Oregon Health and Science University, Portland, OR*

Jason A. Dominitz, MD, MHS, *Associate Professor of Medicine, Division of Gastroenterology, VA Puget Sound Health Care System and University of Washington School of Medicine, Seattle, WA*

Jeffrey Drebin, MD, PhD, FACS, *Department of Surgery and Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA*

Glenn M. Eisen, MD, MPH, *Division of Gastroenterology, Oregon Health and Science University, Portland, OR*

Douglas O. Faigel, MD, FACG, *Associate Professor of Medicine, Director of Endoscopy, Oregon Health and Science University, Portland, OR*

Gregory G. Ginsberg, MD, *Professor of Medicine, Division of Gastroenterology, Director of Endoscopic Services, University of Pennsylvania Health Systems, Philadelphia, PA*

Deepak V. Gopal, MD, FRCP(C), FACP, *Assistant Professor of Medicine, Section of Gastroenterology and Hepatology, University of Wisconsin School of Medicine, Madison, WI*

Takuji Gotoda, MD, *Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan*

William M. Grady, MD, *Assistant Member, Clinical Research Division, Fred Hutchinson Cancer Research Center; Assistant Professor of Medicine, Division of Gastroenterology, University of Washington School of Medicine; Staff Physician, VA Puget Sound Health Care System, Seattle, WA*

Diane Hershock, MD, PhD, *Department of Hematology/Oncology, Abramson Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, PA*

John M. Holland, MD, *Department of Radiation Oncology, Oregon Health and Science University, Portland, OR*

Peter R. Holman, MD, *Division of Hematology/Oncology, University of California, San Diego, CA*

Wendy C. Hsu, MD, *Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA*

Arthur Y. Hung, MD, *Department of Radiation Oncology, Oregon Health and Science University, Portland, OR*

Gordon C. Hunt, MD, *Division of Gastroenterology, University of California, San Diego, CA*

Andrew Ippoliti, MD, *Division of Gastroenterology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA*

Brian C. Jacobson, MD, MPH, *Boston University School of Medicine, Boston Medical Center, Boston, MA*

Sanjay Jagannath, MD, *Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, MD*

Vaman Jakribettuu, MD, *Division of Gastroenterology, University of Colorado Health Sciences Center, Denver, CO*

Michael L. Kochman, MD, FACP, *Professor of Medicine and Surgery, Co-Director Gastrointestinal Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA*

John G. Kuldau, MD, *Division of Gastroenterology, University of California, San Diego, CA*

Marc S. Levine, MD, *Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA*

George A. Makar, MD, *Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA*

KEVIN MCGRATH, MD, *Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA*

JON MORRIS, MD, *Department of Surgery and Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA*

WILLSCOTT E. NAUGLER, MD, *Division of Gastroenterology, University of California, San Diego, CA*

DOUGLAS B. NELSON, MD, *Division of Gastroenterology, Minneapolis VA Medical Center, Professor of Medicine, University of Minnesota, Minneapolis, MN*

IAN D. NORTON, MBBS, PHD, FRACP, *Department of Gastroenterology and Hepatology, Concord Hospital, Sydney, Australia*

GREGORY OLDS, MD, *Division of Gastroenterology, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, OH*

GEORGIOS I. PAPACHRISTOU, MD, *Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA*

GANATHAPY A. PRASAD, MD, *Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL*

MASSIMO RAIMONDO, MD, *Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL*

STEPHEN E. RUBESIN, MD, *Professor of Radiology, University of Pennsylvania School of Medicine and Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA*

THOMAS J. SAVIDES, MD, *Department of Gastroenterology, University of California, San Diego, CA*

MANDEEP S. SAWHNEY, MD, *Division of Gastroenterology, Minneapolis VA Medical Center, Assistant Professor of Medicine, University of Minnesota, Minneapolis, MN*

JAMES M. SCHEIMAN, MD, *Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, MI*

VANESSA M. SHAMI, MD, *Division of Gastroenterology, University of Virginia, Charlottesville, VA*

OMID A. SHAYE, MD, *Division of Gastroenterology, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA*

EVAN S. SIEGELMAN, MD, *Department of Diagnostic Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA*

ADAM SLIVKA, MD, PHD, *Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA*

ROY M. SOETIKNO, MD, *Division of Gastroenterology, Palo Alto VA Medical Center, Palo Alto, CA*

JOHN STROTHER, MD, *Division of Hematology and Oncology, Oregon Health and Science University, Portland, OR*

WEIJING SUN, MD, *Department of Surgery and Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA*

JONATHAN P. TERDIMAN, MD, *Division of Gastroenterology, University of California, San Francisco, CA*

MADHULIKA G. VARMA, MD, *Division of Gastroenterology, University of California, San Francisco, CA*

FERNANDO S. VELAYOS, MD, *Division of Gastroenterology, University of California, San Francisco, CA*

JASON VOLLWEILER, MD, *Department of Gastroenterology and Hepatology, Cleveland Clinic Foundation, Cleveland, OH*

MICHAEL B. WALLACE, MD, MPH, *Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL*

ERIK-JAN WAMSTEKER, MD, *Division of Gastroenterology, University of Michigan Medical Center, Ann Arbor, MI*

KENNETH K. WANG, MD, *Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL*

IRVING WAXMAN, MD, *Section of Gastroenterology, The University of Chicago, Chicago, IL*

STEPHAN M. WILDI, MD, *Division of Gastroenterology, University of Zurich, Switzerland*

TIMOTHY WOODWARD, MD, *Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL*

KENNETH H. YU, MD, *Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA*

GREGORY ZUCCARO, JR., MD, *Department of Gastroenterology and Hepatology, Cleveland Clinic Foundation, Cleveland, OH*

List of Color Plates

ESOPHAGUS

I

1 Barrett's Esophagus

Screening, Diagnosis, and Management

GLENN M. EISEN, MD, MPH

CONTENTS

1. INTRODUCTION

Barrett's esophagus (BE) or columnar lined esophagus, is an acquired condition associated with chronic gastroesophageal reflux disease (GERD). BE is strongly associated with GERD. Numerous endoscopic studies have demonstrated high rates of BE in patients with chronic GERD *(1–3)*. It is a condition in which the normal stratified squamous epithelium of the tubular esophagus is replaced by a metaplastic columnar epithelium. The overriding concern for patients with BE is its malignant potential. BE is accepted as the precursor in most cases of esophageal adenocarcinoma. This malignancy has been linked to chronic GERD and obesity as has BE *(4,5)*. Three case–control studies have demonstrated a strong association between adenocarcinoma of the esophagus and GERD *(4–7)*. The incidence of this malignancy has been rising at a rate of 5–10% for the past three decades in western Europe and the United States, faster than any nondermatological malignancy *(8)*. The Surveillance, Epidemiology, and End Results registry noted more than a 100% increase in the incidence of this tumor between 1976 and 1987 *(9)*. The increasing incidence of esophageal adenocarcinoma appears to be continuing *(10)*. Before the 1970s, esophageal adenocarcinoma accounted for less than 5% of esophageal malignancies. The increased incidence of this lesion is unlikely to be explained by alterations in the use of diagnostic testing (i.e., endoscopy) because this tumor has been found to have a significant male predilection. Also, misclassifying distal esophageal adenocarcinomas as gastric cardiac adenocarcinomas is unlikely to account for this trend because cardia malignancies are increasing in incidence as well. Epidemiological studies have consistently shown esophageal adenocarcinoma to be most common in males (7:1 ratio to females) and whites *(11,12)*.

From: *Endoscopic Oncology: Gastrointestinal Endoscopy and Cancer Management.* Edited by: D. O. Faigel and M. L. Kochman © Humana Press, Totowa, NJ

The prognosis is poor once symptomatic cancer develops, the 5-yr relative survival rate being less than 7%. This dismal prognosis has prompted efforts at endoscopic screening and surveillance, in order to identify earlier staged cancers and dysplastic lesions. There is some preliminary data that suggests that esophageal adenocarcinoma detected by endoscopic surveillance is detected at an earlier stage than when individuals present with dysphagia *(13)*. However, there are currently no randomized clinical trials formally assessing the utility of screening for or surveillance of BE.

2. PATHOGENESIS

2.1. GERD AND BE

It is currently accepted that BE develops as a complication of chronic GERD. The evidence that mucosal injury to the esophagus as a result of GERD can cause BE and lead to adenocarcinoma of the esophagus is compelling *(14,15)*. The estimated prevalence of reflux in the general population is between 25 and 35% (at least one episode per week). Approximately 10–15% of the population experience reflux daily. Overall, it has been estimated that more than 60 million American adults experience reflux symptoms on a regular basis. BE has been identified in 10–20% of individuals undergoing upper endoscopy for reflux symptoms and in 0.4% at autopsy *(16)*. Recent studies have demonstrated a direct correlation between the rates of endoscopy and the discovery of BE *(17)*. The incidence of clinically diagnosed BE (>3 cm) increased 28-fold between 1965–1969 and 1995–1997 in the Olmstead County catchment area, suggesting that the more we look for BE, the more we find. Utilizing these estimates of prevalence, BE may be present in almost 700,000 adults in the United States. It thus appears that GERD is quite common, as it is the development of BE. The concern is that those individuals with BE are at greater risk of developing esophageal adenocarcinoma than the general population.

A recent prospective assessment of asymptomatic male veterans older than 50 yr determined that 25% had BE *(18)*. This finding suggests that many individuals without GERD, or at least subclinical GERD may still develop BE. Lagergren et al. *(4)* also found that in their case–control study of GERD and esophageal adenocarcinoma, 40% of those with this malignancy did not note antecedent GERD. These study results are disconcerting, because screening is currently focused on symptomatic individuals only, and to screen entire populations would be untenable. There appears to be limited familial clustering of BE, accounting for perhaps 10% of all cases *(19,20)*. Nongenetic factors appear to predominate, although satisfactory answers regarding why white males remain the highest risk group remain unknown. Neither tobacco use nor alcohol ingestion are strong risk factors, unlike in the case of squamous cell carcinoma of the esophagus.

2.2. RISK OF ESOPHAGEAL ADENOCARCINOMA

The presence of BE is associated with a risk of developing esophageal adenocarcinoma that is 30–125 times that of the general population *(21)*. However, this relative risk does not correspond with a high absolute risk. The incidence of colorectal cancer remains approx 20-fold higher than the incidence of esophageal adenocarcinoma in the United States *(22)*.

Individuals with BE develop adenocarcinoma at a rate of 0.8–1.3% per year, based on small retrospective and prospective cohorts *(23)*. The natural history of BE progression to cancer is limited to a handful of prospective endoscopic studies comprising 285 patients followed from 1 to 5 yr. Of the 150 patients without dysplasia at study onset, 5 developed cancer over an interval of 3.4–10 yr. There has been significant variation in the reported incidence of BE as well as its progression to esophageal adenocarcinoma. However, the absolute risk may be somewhat overstated owing to publication bias inherent for small cohorts *(24)*. The overall risk appears to be approx 1 per 100 patient-years. It appears that the overall cancer risk is somewhat small, and the majority of patients will not develop esophageal adenocarcinoma. Nevertheless, current guidelines suggest both screening for those at risk and surveillance once BE is detected.

3. DIAGNOSIS AND SURVEILLANCE

3.1. DIAGNOSING BE

BE can be detected on upper endoscopy but must be verified by histological assessment. On endoscopic examination the distal esophageal mucosa appears velvety reddish and extends cephalad from the gastroesophageal junction (GEJ). This mucosa can extend circumferentially or in the form of "tongues" of mucosa. Segments of BE have been somewhat arbitrarily separated into short and long segments, with a long segment considered 3 cm in length or greater *(25)*. Incomplete intestinal metaplasia (IM) of the tubular esophagus is the histological hallmark of BE. Special stains (e.g., Alcian blue) are frequently employed to identify goblet cells indicating IM, which is termed "incomplete" because the clomnuar cells lack a brush border. The endoscopist and pathologist must ascertain that the biopsies do not originate from the proximal stomach *(26)*. Prior studies have found frequent IM at the GEJ, but its significance

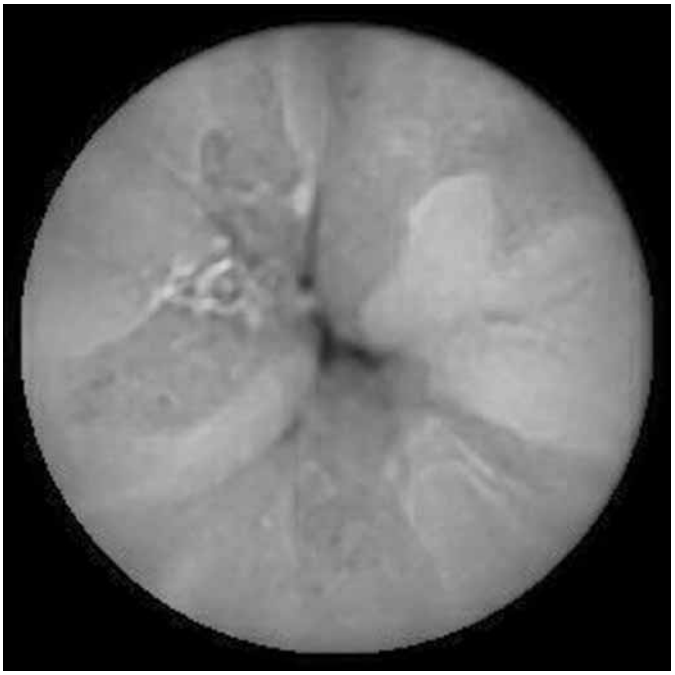


Fig. 1. Capsule endoscopy image of the distal esophagus demonstrating tongues of salmon-colored columnar epithelium consistent with BE.

remains unclear and practice guidelines do not recommend routine biopsies of this area *(27)*. Other types of mucosa have been considered Barrett's epithelium in the past include cardiac and fundic type epithelia. However, these cell types do not appear to have the same malignant potential as intestinal metaplastic tissue and should no longer be considered Barrett's *(28)*.

Other diagnostic modalities such as thin caliber endoscopy and capsule endoscopy have been recently utilized to diagnose BE, but biopsy is not always possible, potentially limiting their utility *(29,30)* (Fig. 1). Barium upper gastrointestinal series should not be utilized for Barrett's screening because of its lack of sensitivity to detect columnar-lined epithelium. Nonendoscopic balloon cytology to retrieve dysplastic or nondysplastic Barrett's epithelium has proved disappointing in research trials and should not be employed in clinical practice *(31)*.

Although not generally validated, standard endoscopic biopsy technique usually involves four quadrant biopsy of the visible Barrett segment at 2-cm intervals, with focused biopsying of any ulceration or raised lesion within the segment. Utilization of jumbo biopsy forceps has been suggested to improve diagnostic yield, but a recent study suggested this technique was just as fallible as standard biopsy forceps in detecting unsuspected malignancy in patients harboring high-grade dysplasia (HGD) *(32)*. A Seattle group has advocated using jumbo biopsy forceps for Q1 cm biopsies as a research technique, but this has not been generally utilized in clinical practice *(33)*.

Other novel endoscopic techniques have been utilized in research settings in the hope of identifying abnormalities within a Barrett's segment rather than relying on the "needle in the haystack" method of random biopsies. Chromoendoscopy using methylene blue has been shown to detect 95% of IM *(34)*.

Magnification endoscopy in addition to methylene blue installation maybe useful in identifying HGD and early cancer in the absence of visible lesions within a Barrett's segment *(35)*. Sharma et al. *(36)* performed chromoendoscopy with indigo carmine staining combined with magnification endoscopy in patients with BE and found the ridge/villous pattern had a 92% positive predictive value for IM. Other techniques have been attempted for detecting either IM and/or dysplasia including fluorescence spectroscopy and optical coherence tomography (*see* Chapter 3). The elusive goal remains to develop a sensitive, noninvasive modality to identify those at high risk for malignancy. Thus far clinical practice has not adopted any of these investigational techniques—continuing to rely on random four-quadrant biopsies of visualized columnar-lined epithelium.

There has been intense interest in developing markers of progression to malignancy in patients with BE. Risk stratification by histology, immunohistochemistry, and molecular pathology has been evaluated. Despite all this research effort, the only currently clinically accepted and utilized marker is dysplasia. This remains a purely morphological term. Riddell et al. *(37)* defined dysplasia as "an unequivocal neoplastic epithelium confined within the glandular basement membrane." The degree of dysplasia is determined based on the degrees of morphological abnormality. Unfortunately, there remains significant interpathologist interpretation variability with κ-scores ranging from 0.43 to 0.66 *(38,39)*. Therefore, a second opinion is warranted, especially in cases in which clinical decision making will be affected.

3.2. SCREENING/SURVEILLANCE OF BE

It appears that most cases of esophageal adenocarcinoma develop through a sequence of cellular changes leading to progressive dysplasia and ultimately carcinoma. This process affords endoscopists the opportunity to detect dysplasia and intervene before the development of malignancy. Current recommendations suggest biannual endoscopic surveillance examinations for individuals with BE. A healthy 30 yr old might be expected to undergo 25 endoscopies over the course of his/her lifetime. Multiply these frequent endoscopies by the estimated 1–2% in the United States with BE and this leads to a significant health expenditure, not to mention the complication risks and loss of work time. Furthermore, this practice, although widely endorsed and utilized, has not been clearly linked to improved patient outcomes.

Updated guidelines for the diagnosis and surveillance of BE were published by the American College of Gastroenterology (ACG) in 2002 *(40)*. Recommendations from two other gastroenterology societies were given during preparation of this document and "incorporated into the final document whenever possible." The recommendation for endoscopic screening states: "patients with chronic GERD symptoms are those most likely to have BE and should undergo upper endoscopy." This guideline remains quite vague, but in general individuals 50 and over with GERD symptoms for 5 or more years should be considered for screening. However, the published clinical guideline permits wide variation in screening practices. A recent AGA consensus conference concluded that there was insufficient evidence to support screening for BE in adults over the age of 50, regardless of the duration of reflux symptoms *(41)*.

Table 1
Surveillance for Barrett's Esophagus *(40)*

Dysplasia	*Documentation*	*Follow-up endoscopy*
None	Two EGDs with biopsy	3 yr
Low grade	Highest grade on repeat	1 yr until no dysplasia
High grade	Repeat EGD with biopsy Expert pathologist confirmation	Focal every 3 mo Multifocal intervention Mucosal irregularity EMR

EGD, esophagogastrodudonoscopy; EMR, endoscopic mucosal resection.

Endoscopic surveillance is recommended in patients with documented BE. These patients are recommended to have two examinations with biopsy. If there is no dysplasia on two consecutive endoscopies with biopsy, then a 3-yr interval from thereon is considered appropriate *(23)* (*see* Table 1). There have been several decision models developed concerning Barrett's screening and surveillance practices. One of the first models only evaluated endoscopic surveillance and determined that endoscopic surveillance every 2–3 yr appears most cost-effective *(42)*. The ACG practice parameters committee has concurred with this determination, but has cited the significant limitations of present data.

Despite the increasing incidence of esophageal adenocarcinoma in the United States and western Europe, the overall cancer rates are still small as demonstrated earlier. Inadomi et al., employing a Markov model and literature-based estimates, found that screening followed by surveillance in BE patients with dysplasia appears economically acceptable with an incremental cost-effectiveness ratio (ICER) of $10,440 compared with no screening. However, surveillance in patients without dysplasia appears prohibitively expensive with ICERs between $381,543 and $596,184, depending on an interval of between q2 and 5 yr *(43)*. These authors questioned the utility of surveillance in patients not demonstrated to have dysplasia.

There are currently no large-scale, multicenter studies evaluating the natural history of BE, severely limiting our ability to make evidence-based decisions on diagnosis, surveillance, and risk stratification. Further, all available research has come from tertiary endoscopy centers potentially biasing the findings.

Once patients with BE develop dysplasia, the risk of cancer increases dramatically. Patients with HGD (who do not have cancer at baseline) have a high risk of progression to cancer of 14–59% during follow-up of 3–7 yr *(44–46)*. The natural history of low-grade or indefinite dysplasia is less certain, with reported rates of progression of neoplasia from 7 to 28% *(47)*. Sampliner analyzed data from five centers that have performed prospective studies from 2.7 to 7.3 yr, finding that 7% of patients with low-grade dysplasia and 2% of patients with no dysplasia developed cancer during follow-up *(23)*.

4. MANAGEMENT OF BE

Theoretically, eliminating the Barrett's epithelium could decrease or eliminate the cancer risk. In addition, the burden for endoscopic surveillance might also diminish. Unfortunately, despite several trials, neither medical (profound acid inhibition) or surgical (fundoplication) therapies appear to achieve complete regression of BE and elimination of its cancer risk *(48–50)*.

Patients diagnosed with advanced dysplasia in a BE segment are advised to undergo more frequent surveillance or esophagectomy, owing to the significant cancer risk. Between 5 and 60% of patients with HGD enrolled in surveillance will develop cancer over 1–7 yr *(51,52)*. Prophylactic esophagectomy has been recommended by many experts for patients with known HGD, because 30 and 40% may already harbor malignancy *(53,54)*. However, esophagectomy is associated with significant morbidity (20–47%) and mortality (average 4%) even at experienced centers *(55,56)*. The results may be more disappointing at other sites, although data is lacking.

Also, some patients with HGD may not be surgical candidates owing to significant comorbidity. It has been estimated that the mean age at diagnosis of Barrett's associated adenocarcinoma is 64 yr old *(57)*. An ideal therapy would be able to eliminate the premalignant epithelium and remove the need for further endoscopic evaluation. Furthermore, this intervention could be targeted for individuals with BE at high risk for developing cancer.

Recently, it has been shown that if the metaplastic epithelium is endoscopically ablated and subsequently healed in an anacid environment, the neoepithelium may become normal squamous mucosa *(58)*. Following this seminal report, there have been numerous small, uncontrolled trials evaluating various ablative methods to eliminate early esophageal adenocarcinoma, dysplastic tissue, and even nondysplastic BE. There has been considerable enthusiasm for these techniques despite the lack of prospective randomized controlled trials to establish their efficacy.

5. CONCLUSIONS

BE is an accepted malignant precursor for esophageal adenocarcinoma. This tumor's incidence has continued to rise at a rapid rate over the past 30 yr. Current practice guidelines recommend screening individuals with chronic GERD symptoms for the presence of BE. These guidelines are somewhat vague and millions of patients fit these criteria for screening. Despite minimal evidence that screening or surveillance is effective, these are the current practice standards.

The number of new cases of cancer of the esophagus in 2003 was 14,250 *(59)*. If we assume that approximately one-half of these cases are adenocarcinoma, there are about 7000 new cases of adenocarcinoma per year. Three recent studies (two population-based studies and a systematic review of the literature) found that less than 7% of patients with adenocarcinoma had known BE prior to the cancer diagnosis *(60,61)*. Surveillance cannot work if the vast majority of patients who ultimately develop cancer are not enrolled in surveillance programs. Despite this, it continues to be endorsed.

Currently, conventional upper endoscopy is recommended as a screening tool, but potentially other modalities, such as small caliber endoscopes and capsule endoscopy, may provide a more cost-effective mechanism for screening. Once BE is diagnosed, by the presence of IM, then surveillance intervals are based on whether dysplasia is present. Medical management includes antisecretory therapy primarily for GERD symptom relief. There are no studies demonstrating that PPI or H2RA therapy eliminates Barrett's metaplasia or cancer risk. This holds true for surgical fundoplication as well. Endoscopic ablation of BE should be reserved for patients with dysplastic epithelium (*see* Chapter 5).

There remain significant information gaps that could aid in our management of patients with BE. Discerning truly high-risk groups for esophageal adenocarcinoma could lead to targeted screening and surveillance. Further work on validating molecular markers for BE progression is necessary as well, given the interobserver variability of dysplasia assessment and its moderate concordance with subsequent neoplasia.

REFERENCES

1. Winters C, Spurling TJ, Chobanian SJ, et al. Barrett's esophagus: A prevalent occult complication of gastroesophageal reflux disease. Gastroenterology 1987; 92:118–124.
2. Lieberman DA, Oehlke M, Helfand M, GORGE Consortium. Risk factors for Barrett's esophagus in community-based practice. Am J Gastroenterol 1997; 92:1293–1297.
3. Eisen GM, Sandler RS, Murray S, Gottfried M. The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. Am J Gastroenterol 1997; 92:27–31.
4. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340(11):825–831.
5. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Int Med 1999; 130(11):883–890.
6. Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraument JF Jr, The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA 1995; 274:474–477.
7. Farrow DC, Vaughan TL, Sweeney C, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists and risk of esophageal and gastric cancer. Cancer Causes Control 2000; 11:231–238.
8. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999; 26(5 Suppl 15):2–8.
9. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1287–1289.
10. Bollschweiler E, Wolfgraten E, Gutschow C, et al. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 2001; 92:549–555.
11. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. Eur J cancer Prev 1992; 1:265–269.
12. Hansson LE, Sparen P, Nyren O. Increasing incidence in both histological types of esophageal carcinoms among men in Sweden. Int J Cancer 1993; 54:402–407.
13. Sampliner RE. Adenocarcinoma of the esophagus and gastric cardia: is there progress in the face of increasing cancer incidence? Ann Int Med 1999; 130(1):67–69.
14. Shaheen N, Ransohoff DF. Gastroesophageal reflux, Barrett esophagus and esophageal cancer. Scientific Review. JAMA 2002; 287:1972–1981.
15. Falk GW. Barrett's esophagus. Gastroenterology 2002; 122:1569–1591.

16. Cameron AJ, Zinsmeister AR, Ballard DJ, et al. Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. Gastroenterology 1990; 99:918–922.
17. Conio, M, Cameron AJ, Romero Y, et al. Secular tends in the epidemiology and outcome of Barrett's oesophagus in Olmsted County, Minnesota. Gut 2001; 48:304–309.
18. Gerson LB, Shetler K, Triadafilopoulos G. Prevalence of Barrett's esophagus in asymptomatic individuals. Gastroenterology 2002; 123(2):461–467.
19. Chak A, Lee T, Kinnard MF, et al. Familial aggregation of Barrett's oesophagus, oesophageal adenocarcinoma and oesophagogastric junctional adenocarcinoma in Caucasian adults. Gut 2002; 51:323–328.
20. Romero Y, Cameron AJ, Locke GR 3rd, et al. Familial aggregation of gastroesophageal reflux in patients with Barrett's esophagus and esophageal adenocarcinoma. Gastroenterology 1997; 113:1449–1456.
21. Spechler SJ, Goyal RK. Barrett's esophagus. N Engl J Med 1986; 315:362–371.
22. Eisen G, Lieberman D, Fennerty MB, Sonnenberg A. Screening and surveillance in Barrett's esophagus: a call to action. Clin Gastroenterol Hepatol. 2004; 2(10):861–864.
23. 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(2):212–215.
24. Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000; 119(2):333–338.
25. Sharma P, Morales TG, sampliner RE. Short segment Barrett's esophagus—the need for standardization of the definition and endoscopic criteria. Am J Gastroenterol 1998; 93:1033–1036.
26. Paull A, Trier JS, Dalton MD, et al. The histologic spectrum of Barrett's esophagus. N Engl J Med 1976; 295:476–480.
27. Spechler SJ. Intestinal metaplasia at the gastroesophageal junction. Gastroenterology 2004; 126(2):567–575.
28. Haggitt RC. Adenocarcinoma in Barrett's esophagus: a new epidemic? Hum Pathol 1992; 23:475–476.
29. Eliakim R, Yassin K, Shlomi I, et al. A novel diagnostic tool for detecting oesophageal pathology: the PillCam oesophageal video capsule. Aliment Pharmacol Ther 2004; 20(10):1083–1089.
30. Sorbi D, Gostout CJ, Henry J, Lindor KD. Unsedated small-caliber esophagogastroduodenoscopy (EGD) versus conventional EGD: a comparative study.Gastroenterology 1999; 117(6):1301–1307.
31. Falk GW, Chittajallu R, Goldblum R, et al. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. Gastroenterology 1997; 112(6):1787–1797.
32. 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(2):170–176.
33. 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; 102:1212–1219.
34. Canto MI, Setrakian S, Petras R, et al. Methylene blue selectively stains intestinal metaplasia in Barrett's esophagus. Gastrointest Endosc 1996; 44:1–6.
35. Yagi K, Nagamura A, Sekine A. Accuracy of magnifying endoscpy with methylene blue in the diagnosis of specialized intestinal metaplasia and short-segment Barrett's esophagus in Japanese patients without *Helicobacter pylori* infection. Gastrointest Endosc 2003; 58–65.
36. Sharma P, Weston AP, Topalovski M, et al. Magnification chromoendoscopy for the detection of intestinal metaplssia and dysplasia in Barrett's oesophagus. Gut 2003; 52:24–27.
37. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications, Hum Pathol 1983; 14:931–968.
38. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol 2001; 32:368–378.
39. Alikhan M, Rex D, Khan A, et al. Variable pathologic interpretation of columnar lined esophagus by general pathologists in community practice. Gastrointest Endosc 1999; 50:23–26.
40. Sampliner RE. Updated guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2002; 97: 1888–1895.
41. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago workshop. Gastroenterology 2004; 127:310–330.
42. Provenzale D, Kemp JA, Arora S, et al. A guide for surveillance of patients with Barrett's esophagus. Am J Gastroenterol 1994; 89:670–680.
43. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett's esophagus in high-risk populations: A cost-utility analysis. Ann Intern Med 2003; 138:176–186.
44. Reid BJ, Levine DS, Longton G, et al. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low and high-risk patient subsets. Am J Gastroenterol 2000; 95:1669–1676.
45. Buttar NS, Wang KK, Sebo TJ, et al. Extent of high grade dyaplasia in Barrett's esophagus correlates with risk of adenocarcinoma. Gastroenterology 2001; 120:1630–1639.
46. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term management of Barrett's esophagus with high grade dysplasia. Gastroenterology 2001; 120:1607–1619.
47. Falk GW. Barrett's esophagus. Gastroenterology 2002; 122:1569–1591.
48. Gore S, Healey CJ, Sutton R, et al. Regression of columnar lined (Barrett's) oesophagus with continuous omeprazole therapy. Aliment Pharmacol Ther 1993; 7:623–628.
49. Sampliner RE, Garewal HS, Fennerty MB, Aickin M. Lack of impact of therapy on extent of Barrett's esophagus in 67 patients. Dig Dis Sci 1990; 35:93–96.
50. Sharma P, Sampliner RE, Camargo E. Normalization of esophageal pH with high dose proton pump inhibitor therapy does not result in regression of Barrett's esophagus. Am J Gastroenterol 1997; 92(4):582–585.
51. Reid BJ, Levine DS, Longton G, Blount PL, Rabinovitch PS. Predictors of progression to cancer in Barrett's esophagus: baseline histology and flow cytometry identify low-high risk patients subsets. Am J Gastroenterol 2000; 95:1669–1676.
52. Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high grade dysplasia. Gastroenterology 2001; 120:1607–1619.
53. Pera M, Trastek VF, Carpenter HA, Allen MS, Deschamps C, Pairolero PC. Barrett's esophagus with high grade dysplasia: an indication for esophagectomy? Ann Thorac Surg 1992; 54:199–204.
54. Rice TW, Falk GW, Achar E, Petras RE. Surgical management of high grade dysplasia in Barrett's esophagus. Am J Gastroenterol 1993; 88:1832–1836.
55. Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons patient care evaluation study. J Am Coll Surg 2000; 190:548–559.
56. Heitmiller RF, Redmond M. Hamilton SR. Barrett's esophagus with high grade dysplasia. Ann Surg 1996; 224:66–71.
57. Cameron AJ, Lomboy CT. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. Gastroenterology 1992; 103:1241–1245.
58. Sampliner RE, Hixson LJ, Fennerty MB, Garewal HS. Regression of Barrett's esophagus by laser ablation in an anacid environment. Dig Dis Sci 1993; 38(2):365–368.
59. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer Statistics 2003. CA Cancer J Clin 2003; 53:5–26.
60. Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: A population-based study. Gastroenterology 2002; 122:633–640.
61. Dulai GS, Guha S, Kahn KL, Gornbein J, Weinstein WM. Preoperative prelvalence of Barrett's esophagus in esophageal adenocarcinoma: A systematic review. Gastroenterology 2002; 122:26–33.

2 Endoscopic Screening for Squamous Cell Carcinoma of the Esophagus

Brian C. Jacobson, MD, MPH

Contents

1. INTRODUCTION

Although the relative incidence of esophageal squamous cell carcinoma (SCC) has been declining steadily in the United States and Europe compared to that of adenocarcinoma *(1,2)*; esophageal SCC continues to be the more common form of esophageal malignancy worldwide *(3)*. There are approx 6000 new cases of esophageal SCC diagnosed in the United States annually *(4)*. The global incidence and gender ratio vary widely according to geographic region, likely reflecting environmental and dietary factors more than genetic predisposition. Several risk factors for esophageal SCC have been identified, making screening a potential option for specific populations. This chapter outlines conditions or behaviors that are strongly associated with this malignancy, describes methods for improving the endoscopic detection of early squamous cell dysplasia, and suggests specific instances in which screening for esophageal SCC may be appropriate.

2. RATIONALE FOR SCREENING

In general, screening for a disease should be undertaken when early detection will result in improved patient survival or quality of life. Typically, the number of people deriving benefit from screening for a malignancy is small, whereas the majority of those screened face potential morbidity, both physical and psychological, from screening procedures *(5)*. It is for this reason that screening is often reserved for specific high-risk populations. For instance, current guidelines recommend screening endoscopy for Barrett's esophagus among patients with chronic gastroesophageal reflux disease, and for surveillance endoscopy for dysplasia among those with known Barrett's esophagus *(6,7)*, even though the annual incidence of esophageal adenocarcinoma among those with Barrett's esophagus is approx 0.4–0.5% *(8–12)*. Screening for esophageal SCC, however, has not been widely advocated despite the high mortality associated with this malignancy *(13)*. Long-term survival correlates directly with stage at diagnosis *(14)*, suggesting that detection of very early cases should improve outcomes. The infrequency of esophageal SCC makes population-based screening inappropriate. Nonetheless, certain individuals with an increased risk for SCC of the esophagus exist (Table 1), and an understanding of their risk may help guide clinicians and patients in making decisions about screening and surveillance.

3. HIGH-RISK ASSOCIATIONS

3.1. RACE, GENDER, AND GEOGRAPHIC ASSOCIATIONS

Based on data in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry, black men in the United States have a nearly fivefold greater annual risk for developing esophageal SCC than non-Hispanic white men *(15)*. Black women have a twofold greater risk compared with non-Hispanic white men, and a nearly fourfold greater risk compared with women of all other races and ethnicities *(15)*. Asian men are also at increased risk, having twice the incidence as non-Hispanic white men. Particular regions of the world have also been identified in which the incidence of esophageal SCC is extremely high, approaching 1 case per 1000 adults *(16)*. These locations include eastern Turkey, northern Iran and Afghanistan, southern regions of the former Soviet Union including Turkmenistan and Uzbekistan, northern China and India, regions of Brazil, Argentina, and Uruguay, and the Transkei region of Cape Province and Kenya *(3,16)*. These demographic

From: *Endoscopic Oncology: Gastrointestinal Endoscopy and Cancer Management.* Edited by: D. O. Faigel and M. L. Kochman © Humana Press, Totowa, NJ

Table 1
Conditions or Exposures Strongly Associated With Esophageal SCC

Condition or exposure	*Relative risk for esophageal SCC*
Chronic alcohol use	+ + +
Chronic tobacco use	+ +
Poverty	+
Current or prior cancer of the upper aerodigestive tract	+ + + +
Caustic esophageal stricture	+ + +
Tylosis (type A)	+ + + + +
Achalasia	+

and geographic associations are most likely explained by environmental exposures, such as tobacco, alcohol, and particular dietary factors (discussed later), although differences in susceptibility to exposures may still account for some of these observations *(17)*.

3.2. CHRONIC TOBACCO AND ALCOHOL USE

As many as 80–90% of cases of esophageal SCC can be attributed to tobacco and alcohol use *(14,16)*. The risk associated with cigarette smoking increases directly with increasing pack-years of exposure, with those smoking more than 54 pack-years having a relative risk that is sixfold higher than nonsmokers *(18)*. Former smokers continue to have an increased risk, although this begins to improve in the second decade after cessation. It is postulated that several components of tobacco products, such as nitrosamines, aromatic amines, aldehydes, and phenols have direct carcinogenic effects *(3)*. These may be ingested as tobacco condensates, and thereby come into direct contact with esophageal mucosa *(19)*. Alcohol consumption also demonstrates a dose-dependent increase in risk, with those consuming more than 30 drinks per week having a greater than sevenfold increased risk over nondrinkers *(18)*. Liquor and beer are likely associated with a greater risk than wine, although overall quantity of alcohol consumed may be more important than the specific form *(20)*. The combined, chronic use of large amounts of alcohol and tobacco appears to confer the greatest risk for esophageal SCC, and likely identifies one of the largest at-risk populations in the United States.

3.3. PREVIOUS SCC OF THE UPPER AERODIGESTIVE TRACT

Esophageal SCC is often associated with synchronous or metachronous SCC of the head and neck. The reported incidence of an esophageal SCC associated with a current or prior cancer of the upper aerodigestive tract ranges from 3.7 to 30% *(16,21)*. This variation in rates is likely explained by differences in populations studied and their differing duration of follow-up. A synchronous esophageal SCC has also been found in up to 31% of resected esophageal specimens, many of which were confined to the mucosa or submucosa *(22,23)*. In one prospective study, 14% of patients undergoing endoscopic mucosal resection for early stage (mucosal or submucosal involvement) esophageal SCC were found to develop metachronous esophageal SCC between 14 and 58 mo post-treatment *(24)*. In addition, among patients with esophageal SCC, surveillance pharyngolaryngoscopy can frequently detect metachronous head and neck cancers *(25)*. These findings have lent support to the "field effect" theory, suggesting that the entire squamous epithelium of the upper aerodigestive tract in susceptible individuals is at high risk of malignancy after prolonged exposure to some damaging agent. However, in another prospective study investigators systematically screened 331 men with *any* current or prior nonesophageal cancer, not necessarily upper aerodigestive tract SCC, and found 2.7% harbored esophageal SCC *(26)*. Even after excluding 51 patients with head and neck cancer, the prevalence of esophageal SCC in that study was still 2.1%, a number higher than expected. This suggests that individuals who have experienced any form of cancer may be at increased risk for esophageal SCC.

3.4. DIETARY FACTORS AND POOR SOCIOECONOMIC STATUS

The consumption of salt-pickled or cured foods, sun-dried foods, moldy foods, and smoked fish have all been associated with esophageal SCC *(16)*. It is postulated that these foods expose the esophageal mucosa to high levels of carcinogenic *N*-nitroso compounds or fungal toxins. In addition, diets deficient in fruits, vegetables, zinc, vitamins A, C, E, niacin, and riboflavin, and other micronutrients have also been associated with an increased risk of esophageal SCC *(16)*. Iron deficiency may be associated with esophageal SCC in connection with the Plummer-Vinson syndrome, a combination of iron deficiency anemia and a cervical esophageal web *(16,27)*. Unfortunately, the relative risks associated with specific nutrient exposures or deficiencies have not been well established and dietary questionnaires would likely be impractical for identifying individuals for screening endoscopy. A more useful distinction arises from a condition closely associated with poor nutritional status, namely low socioeconomic status. Poverty has been strongly linked with esophageal SCC *(18,28)*, and may represent a more meaningful way to risk-stratify individuals when considering specific populations for screening.

Another interesting dietary factor that has been associated with esophageal SCC is the frequent consumption of extremely hot beverages, a practice common in regions of Central and South America, China, Iran, and India *(16)*. One such beverage, mate, is an infusion of the herb *Ilex paraguayensis* that is often consumed at extremely hot temperatures. This drink, popular in parts of Argentina, Uruguay, Paraguay, and Brazil, results in thermal esophagitis *(29)*, and it is only those who drink hot mate (as opposed to warm mate), that appear to have increased cancer risk *(30)*. It is therefore the thermal injury from this practice that has been postulated to result in dysplastic changes of the esophagus. In fact, consumption of extremely hot tea and coffee have also been linked to esophageal SCC *(31)*.

3.5. CAUSTIC INGESTION

The risk for developing esophageal cancer in the setting of an esophageal stricture following caustic ingestion is increased 1000-fold compared with the general population *(7)*. The reported interval between ingestion of a caustic substance (e.g., lye) and the subsequent development of cancer ranges from 14 to 47 yr, and the tumor typically develops within the stricture itself. The mechanism of increased risk is unknown, but may relate to chronic inflammation within the stricture.

3.6. ACHALASIA

Achalasia is a condition of unknown etiology in which there is loss of neurons within the esophageal wall and lower esophageal sphincter. It is clinically manifested by dysphagia to both solid food and liquids, with eventual dilation of the esophagus and chronic stasis of ingested foods. It is this stasis and subsequent inflammation that is postulated to impart an increased risk of esophageal cancer to those with achalasia. This risk has been estimated to be 7- to 33-fold greater than normal, and includes risks for adenocarcinoma and, more commonly, SCC *(16)*. One prospective, *hospital-based* study followed 195 patients with achalasia with periodic endoscopy for a total follow-up of 874 person-years *(32)*. During that time three patients developed esophageal SCC a mean of 5.4 yr after their diagnosis of achalasia. This cancer incidence of 3.4 per 1000 patients per year was significantly higher than that expected in the general population. Two of the three patients demonstrated long-term survival after treatment for their cancer. The only prospective, *population-based* study to address this issue included 1062 patients with a combined total of 9864 yr of follow-up *(33)*. These patients, however, were not necessarily enrolled in a cancer surveillance program. Excluding cases likely present at study entry, the incidence of cancer was 20-fold greater among men and eightfold greater among women with achalasia compared with the general population. Of the 24 cases of cancer reported in that study, 14 were SCC, 6 were adenocarcinoma, and 4 were undifferentiated. Previous reports had suggested that cancer risk rises 15–20 yr after symptoms of achalasia first develop *(16)*. However, in the prospective, population-based study the risks were similar for each time frame after initial diagnosis examined (1–4, 5–9, and 10–24 yr) *(33)*. This suggests that surveillance, if advocated, should begin immediately after diagnosis. The frequency and cost-effectiveness of endoscopic surveillance in achalasia has not been determined. Whether definitive therapy for achalasia (e.g., surgical myotomy) changes cancer risk has also not been determined.

3.7. TYLOSIS (DIFFUSE PALMOPLANTAR KERATODERMA)

This rare, autosomal-dominant, fully penetrant condition is marked by hyperkeratosis of the palms and soles, in addition to a thickening of the oral and esophageal mucosa. Two phenotypes, A and B, have been identified and appear to be linked to mutations in keratin genes clustered on chromosomes 17q23 and 12q11–q13, respectively *(34,35)*. Type B presents in infancy, is associated with gingival hyperplasia, and regions of hyperkeratosis have sharply demarcated edges that can extend onto wrist flexures *(36)*. This form has not been associated with an increased risk of esophageal cancer. In contrast, type A presents in childhood to young adulthood and is associated with buccal leukoplakia and regions of hyperkeratosis that have blurred edges that can affect weight-bearing regions *(36)*. Patients with type A tylosis have an extremely high risk of developing SCC of the esophagus, with a 50% incidence by age 45 and a more than 90% incidence by age 65 *(37)*. Early dysplasia may be endoscopically invisible, suggesting surveillance biopsies should be taken from multiple sites at various levels of the esophagus.

3.8. RADIATION THERAPY TO THE CHEST

There is a fivefold increased risk of esophageal SCC 10 or more years after radiation therapy for breast cancer compared with women who did not receive radiation therapy for their breast cancer *(38)*. However, the overall risk in this setting is still low, with one study documenting only 72 primary esophageal SCCs among 220,000 women with more than 1 million person-years of follow-up *(38)*.

3.9. LICHEN PLANUS

Lichen planus is a disease of unknown etiology in which there is T-lymphocyte-mediated inflammation directed against the squamous epithelium of the skin, mouth, esophagus, genitals, and anus *(39)*. In mucocutaneous regions, including the esophagus, lichen planus may manifest as lacelike striae or papular, atrophic, plaque-like, or erosive lesions. Patients with liver disease, including hepatitis C, are at increased risk for this condition, although a pathophysiological mechanism explaining the association remains undefined *(40)*. External skin lesions often resolve within 1–2 yr, but lesions of mucus membranes can persist for decades. Patients with oropharyngeal lichen planus are at increased risk for developing SCC, although the risk appears to be less than 1% *(41)*. There is a single report of a person with chronic esophageal lichen planus developing advanced esophageal SCC despite undergoing annual upper endoscopy *(42)*. That patient was neither a smoker nor a regular user of alcohol, increasing the likelihood that the etiology of her SCC was chronic inflammation associated with lichen planus. The authors of that report suggest regular surveillance for dysplasia for anyone with esophageal lichen planus, although there is no evidence proving the effectiveness of this strategy.

4. METHODS FOR IMPROVING THE ENDOSCOPIC DETECTION OF DYSPLASIA

When performing endoscopy for the early detection of malignancy, any suspicious lesion should be biopsied, with consideration given to taking multiple pieces using large-size (jumbo) biopsy forceps for maximum sensitivity *(43)*. The addition of brush cytology may also improve the diagnostic yield *(44,45)*. However, esophageal SCC most likely develops through a dysplasia–neoplasia sequence similar to other forms of cancer *(3)*. This implies that there are microscopic changes, such as nuclear enlargement and clumping of chromatin, that are present before the development of endoscopically visible lesions. The development of improved endoscopic optics along with the use of special mucosal stains (termed "chromoendoscopy") has proven useful for making these lesions visible during endoscopy. These enhancements may allow an endoscopist to target biopsies, thereby making screening or surveillance procedures more efficient.

4.1. MAGNIFICATION ENDOSCOPY

Magnifying endoscopes use various lenses to enlarge an already high-resolution video image. By using special dials on the endoscope handle, the endoscopist can "zoom in" on an image, magnifying it 1.5–105 times the original size *(46)*. This feature has been used with chromoendoscopy (*see* Section 4.2.) to characterize Barrett's epithelium *(47,48)*, small bowel atrophy

in patients with suspected malabsorption *(49)*, colonic polyps, and aberrant crypt foci *(50,51)*.

4.2. CHROMOENDOSCOPY

Chromoendoscopy is the term describing the use of special dyes during endoscopy to highlight histological changes within the gastrointestinal mucosa. A specific dye is applied to the mucosa, typically with the use of a spray catheter passed through the accessory channel of an endoscope. After the application of the dye, careful endoscopic inspection is performed looking for areas that either fails to stain or stain differently than their surroundings. The dye used is chosen based on the particular pathology sought and the choice reflects the different cell types and cell components stained by each dye. In the case of squamous cell dysplasia, iodine is used as the stain based on a chemical reaction between iodine and glycogen *(52)*. The glycogen rich prickle-cell layer of the stratified squamous esophageal epithelium stains greenish brown after the application of a potassium iodide solution or Lugol's iodine. Dysplastic epithelium lacks the glycogen-rich granules in the prickle-cell layer and therefore fails to stain. The brown staining of the normal squamous cells may not be complete but the endoscopist can take biopsies targeted from the least stained regions. Iodine chromoendoscopy can detect early SCC in the esophagus that might otherwise go undetected by conventional endoscopy *(52,53)*. Iodine chromoendoscopy can also be helpful in defining the extent of an esophageal SCC or in better defining the gastroesophageal junction. To perform iodine chromoendoscopy, the esophageal mucosa is typically washed with 40–50 cc of water to remove mucus followed by the application of 10–20 cc of 1.5–3% Lugol's solution. The endoscopist should then wait 1–5 min to ensure sufficient staining before careful inspection. Biopsies are generally taken from unstained or understained regions 5 mm or greater in diameter. Patients may experience heartburn, chest discomfort, dysphagia, fever, tingling, or nausea and the technique should be avoided in those with an allergy to iodine *(52,53)*.

4.3. SPECTROSCOPY AND OPTICAL COHERENCE TOMOGRAPHY

Currently the identification of dysplastic or neoplastic epithelium depends on the histological interpretation of a biopsy specimen by a pathologist. Unfortunately, because normal-appearing epithelium may still harbor dysplasia, "blind" biopsy protocols are still the most commonly used method of tissue sampling during surveillance endoscopy. Yet even the most widely advocated systematic approach using jumbo biopsy forceps can miss adenocarcinoma in the setting of Barrett's esophagus *(54)*. Furthermore, there is significant interobserver variation among pathologists classifying degrees of dysplasia within histological specimens of Barrett's esophagus *(55,56)*. This has led investigators to search for alternative methods for identifying dysplasia that do not rely on tissue processing and histological interpretation. Spectroscopy and optical coherence tomography are two such techniques. They provide information about a tissue using optical technology without the need for taking a biopsy.

Spectroscopy relies on the fluorescent properties of inherent tissue components (fluorescence spectroscopy), the photon-scattering and color-absorption properties of living tissue (light-scattering spectroscopy), and the vibration patterns of specific biological agents (Raman spectroscopy) to aid in the diagnosis of dysplastic foci *(57)*. Optical coherence tomography uses the reflection of infrared light off of living tissue to generate an image similar to that obtained by standard histological processing of a biopsy specimen with 10 μ resolution *(58)*. Although early in clinical applications, these methods are demonstrating great promise for the early detection of esophageal dysplasia *(59,60)*.

5. EFFECTIVENESS OF SCREENING

In some institutions, iodine chromoendoscopy is performed routinely at the end of upper endoscopy for all male patients over the age of 50 *(52)*. This may be appropriate in regions of the world where esophageal SCC is extremely prevalent, but there is no data to support this type of routine use in most locations. However, several investigators have prospectively studied the selective use of upper endoscopy to evaluate specific patients considered to have increased risk for esophageal SCC *(24,26,61–71)*. These patient populations have included those with a history of upper aerodigestive tract malignancy, those with *any* prior malignancy, and those with chronic alcohol/tobacco exposure (Table 2). Some authors regularly performed iodine chromoendoscopy for screening/surveillance, whereas others either used iodine staining selectively, or not at all. When chromoendoscopy was regularly used, there were frequently lesions detected only after the application of Lugol's iodine, supporting its utility in screening. Among a combined total of 3036 patients with a history of current or prior head and neck cancer undergoing screening/surveillance endoscopy, 153 (5%) were found to have either high-grade dysplasia or a synchronous or metachronous esophageal SCC, many of which were confined to the mucosa or submucosa. Among 1504 patients with a history of excessive alcohol use, either alone or in combination with tobacco and hot mate consumption, 60 (4%) were found to have high-grade dysplasia or SCC, many of which were likewise early stage. Given the association between alcohol, smoking, and cancers of the head and neck, it is impossible to determine the exact contribution of each component to the development of esophageal SCC. In addition, the vast majority of patients screened have been male, leaving the utility of screening among women impossible to determine. Nonetheless, a 4–5% yield of dysplasia for a screening endoscopic procedure is quite high and suggests these specific patient populations may benefit from the implementation of a formal screening protocol.

There are, however, different yields between screening (an initial endoscopy) and surveillance (repeat endoscopies over some time interval) endoscopies, with most studies showing that the largest benefit comes an initial screening examination. Different patterns of iodine staining have been noted that may help further risk-stratify patients into those who are more likely to progress to cancer, and therefore more likely to benefit from repeated endoscopy *(24)*. Patients whose esophagus contains numerous tiny (<5 mm) foci of mucosa that fails to stain with iodine appear to be more likely to develop cancer during follow-up *(24,26)*. The yield of iodine chromoendoscopy surveillance in the setting of achalasia has not been reported.

Table 2
Prospective Studies of Screening for Esophageal SCC Among High-Risk Populations

Author	*High-risk association*	*No. of patients*	*Male (%)*	*No. of subjects with high-grade dysplasia or cancer (%)*	*No. of subjects with early-stage[a] lesions (%)*
Shiozaki *(67)*	H&N Ca	178	77	9 (5.1)	7 (78)
Ina *(64)*	H&N Ca	127	100	8 (6.3)	NR
Muto *(65)*	H&N Ca	389	83	54 (13.9)	50 (93)
Petit *(66)*	H&N Ca	1560	NR	50 (3.2)	NR
Scherubl *(68)*	H&N Ca	148	72	15 (10.1)	10 (67)
Atabek *(62)*	H&N Ca	574	NR	12 (2.1)	NR
Tincani *(70)*	H&N Ca and excessive alcohol/tobacco	60	92	5 (8.3)	5 (100)
Shimizu *(26)*	Prior nonesophageal cancer[b]	331	100	9 (2.7)	9 (100)
Shimizu *(24)*	Prior esophageal SCC	82	93	12 (14.6)	12 (100)
Yokoyama *(71)*	Excessive alcohol	901	100	33 (3.7)	31 (94)
Ban *(61)*	Excessive alcohol	255	100	10 (3.9)	10 (100)
Meyer *(69)*	Excessive alcohol and/or smoking[b]	158	96	13 (8.2)	NR
Fagundes *(63)*	Excessive alcohol, smoking, and hot mate drinking	190	100	4 (2.1)	NR

H&N Ca, head and neck cancer; NR, not reported.
[a]Early-stage, high-grade dysplasia or stage I cancer (confined to the mucosa or submucosa without lymph node metastases) *(73)*.
[b]An unreported percentage of subjects also had head and neck cancer.
Note: All studies except Petit, Scherubl, and Atabek reported the routine use of Lugol's iodine chromoendoscopy.

It is extremely important to clarify the definition of effective screening. If one's aim is to simply identify cancer, the data in Table 2 suggest a reasonably high yield for screening endoscopy among patients with head and neck cancer or excessive alcohol and tobacco use. However, when determining the utility of a screening test for malignancy, one should also consider the impact of identifying early cancer on the patient's survival and quality of life. In the case of esophageal SCC, definitive treatment of early-stage lesions can certainly improve survival, but among the patients for whom screening may detect these lesions, overall survival may still be limited. For example, among patients with cancer of the head and neck, a sizeable portion will die from recurrence of this tumor, regardless of therapy for an incidentally identified esophageal cancer. In some cases, surgery for head and neck cancer may limit a surgeon's ability to resect an esophageal cancer, leaving only nonoperative therapeutic options. Finally, patients with chronic alcohol and tobacco exposure are likely to have comorbidities such as cirrhosis or heart disease that predispose to early mortality or limit treatment options for cancer. Therefore, the effectiveness in identifying early esophageal SCC may be limited by an unchanged life expectancy. Two studies of more than 3500 patients with head and neck cancer failed to find much survival benefit from endoscopic screening for esophageal carcinoma *(62,66)*. However, several of the deaths in those series were from esophageal cancer and iodine chromoendoscopy was not routinely used in screening. Therefore very early, otherwise curable lesions may have been underdiagnosed. The question of whether long-term survival can be improved among high-risk populations undergoing optimized screening remains unanswered.

6. CONCLUSIONS AND RECOMMENDATIONS

Although certain exposures significantly increase the risk of developing esophageal SCC, the overall prevalence of this disease should be considered when deciding who might benefit from endoscopic screening. It is probably a combination of factors that conveys the highest risks, and physicians must determine on an individual basis whether screening endoscopy might have a potential impact on a given patient's course. For instance, an impoverished 60-yr-old black man with a long history of alcohol and tobacco use may benefit from a screening endoscopy with iodine chromoendoscopy, whereas a wealthy 60-yr-old nonsmoking white woman who drinks alcohol only occasionally is unlikely to dervie any benefit from screening. Others who may benefit include patients with an early-stage head and neck cancer or patients from a region of the world where the incidence of esophageal SCC is very high. Only patients who can be effectively treated for esophageal cancer should be screened, although early cancers may be amenable to endoscopic mucosal resection in otherwise inoperable patients *(72)*.

According to the American Society for Gastrointestinal Endoscopy (ASGE), patients with tylosis should begin surveillance endoscopy at age 30 and have repeat endoscopy not more than every 1–3 yr *(7)*. This should be limited to patients with type A tylosis. The ASGE also recommends that patients with a history of caustic ingestion with stricture formation undergo endoscopic screening beginning 15–20 yr after the ingestion with surveillance endoscopy not more than every 1–3 yr *(7)*. A role for endoscopic screening among patients with achalasia is less clear, although patients with a prolonged history of dysphagia before diagnosis and treatment may derive benefit. Patients with longstanding esophageal lichen planus may benefit

from screening and surveillance, but this remains speculative. There is insufficient evidence to support a role for screening among patients with a history of radiation therapy to the chest. Finally, the cost-effectiveness of endoscopic screening for esophageal SCC among any high-risk population has not been established.

REFERENCES

1. Devesa S, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998; 83:2049–2053.
2. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. Int J Epidemiol 2000; 29:645–654.
3. Stoner GD, Gupta A. Etiology and chemoprevention of esophageal squamous cell carcinoma. Carcinogenesis 2001; 22:1737–1746.
4. Jemal A, Tiwari RC, Murray T, et al. Cancer Statistics, 2004. CA Cancer J Clin 2004; 54:8–29.
5. Cullen J, Schwartz MD, Lawrence WF, Selby JV, Mandelblatt JS. Short-Term Impact of Cancer Prevention and Screening Activities on Quality of Life. J Clin Oncol 2004; 22:943–952.
6. Sampliner RE. Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 1998; 93:1028–1032.
7. American Society for Gastrointestinal Endoscopy. The role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal tract. Gastrointest Endosc 1998; 48:663–668.
8. Cameron A, Ott B, Payne W. The incidence of adenocarcinoma in columnar-lined (Barrett's) esophagus. N Engl J Med 1985; 313:857–859.
9. Murray L, Watson P, Johnston B, SLoan J, Mainie I, Gavin A. Risk of adenocarcinoma in Barrett's esophagus: population based study. BMJ 2003; 327:534–535.
10. Shaheen N, Crosby M, Bozymski E, Sandler R. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology 2000; 119:333–338.
11. Spechler S, 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; 285:2331–2338.
12. Spechler SJ, Robbins AH, Rubins HB, et al. Adenocarcinoma and Barrett's esophagus: an overrated risk? Gastroenterology 1984; 87:927–933.
13. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999; 83:18–29.
14. Enzinger P, Mayer R. Esophageal cancer. N Engl J Med 2003; 349:2241–2252.
15. Kubo A, Corley DA. Marked multi-ethnic variation of esophageal and gastric cardia carcinomas within the United States. Am J Gastroenterol 2004; 99:582–588.
16. Ribeiro U, Posner MC, Safatle-Ribeiro AV, Reynolds JC. Risk factors for squamous cell carcinoma of the esophagus. Br J Surg 1996; 83:1174–1185.
17. Brown LM, Hoover RN, Greenberg RS, et al. Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? J Natl Cancer Inst 1994; 86:1340–1345.
18. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Can Inst 1997; 89:1277–1284.
19. De Stefani E, Barrios E, Fierro L. Black (air-cured) and blond (flue-cured) tobacco and cancer risk. III: Oesophageal cancer. Eur J Cancer 1993; 29A:763–766.
20. Brown LM, Hoover RN, Gridely G, et al. Drinking practices and risk of squamous-cell esophageal cancer among black and white men in the United States. Cancer Cause Control 1997; 8:605–609.
21. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Synchronous and Metachronous Squamous Cell Carcinomas of the Head and Neck Mucosal Sites. J Clin Oncol 2001; 19:1358–1362.
22. Kuwano H, Ohno S, Matsuda H, Mori M, Sugimachi K. Serial histologic evaluation of multiple primary squamous cell carcinomas of the esophagus. Cancer 1988; 61:1635–1638.
23. Pesko P, Rakic S, Milicevic M, Bulajic P, Gerzic Z. Prevalence and clinicopathologic features of multiple squamous cell carcinoma of the esophagus. Cancer 1994; 73:2687–2690.
24. Shimizu Y, Tukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Metachronous squamous cell carcinoma of the esophagus arising after endoscopic mucosal resection. Gastrointest Endosc 2001; 54:190–194.
25. Watanabe A, Hosokawa M, Taniguchi M, Sasaki S. Periodic pharyngolaryngoscopy detects early head and neck cancer and improves survival in esophageal cancer. Ann Thorac Surg 2003; 76:1699–1705.
26. Shimizu Y, Tukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Endoscopic screening for early esophageal cancer by iodine staining in patients with other current or prior primary cancers. Gastrointest Endosc 2001; 53:1–5.
27. Larsson LG, Sandstrom A, Westling P. Relationship of Plummer-Vinson disease to cancer of the upper alimentary tract in Sweden. Cancer Res 1975; 35:3308–3316.
28. Brown LM, Hoover RN, Silverman DT, et al. Excess Incidence of Squamous Cell Esophageal Cancer among US Black Men: Role of Social Class and Other Risk Factors. Am J Epidemiol 2001; 153:114–122.
29. Munoz N, Victora CG, Crespi M, Saul C, Braga NM, Correa P. Hot mate drinking and precancerous lesions of the esophagus: an endoscopic survey in southern Brazil. Int J Cancer 1987; 39:708–709.
30. Castelletto R, Castellsague X, Munoz N, Iscovich J, Chopita N, Jmelnitsky A. Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. Cancer Epidemiol Biomarkers Prev 1994; 3:557–564.
31. Castellsague X, Munoz N, De Stefani E, Victora CG, Castelletto R, Rolon PA. Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. Int J Cancer 2000; 88:658–664.
32. Meijssen MAC, Tilanus HW, van Blankenstein M, Hop WCJ, Ong GL. Achalasia compicated by oesophageal squamous cell carcinoma: a prospective study in 195 patients. Gut 1992; 33:155–158.
33. Sandler RS, Nyren O, Ekbom A, Eisen GM, Yuen J, Josefsson S. The risk of esophageal cancer in patients with achalasia: a population-based study. JAMA 1995; 274:1359–1362.
34. Risk JM, Field EA, Field JK, et al. Tylosis esophageal cancer mapped. Nat Genet 1994; 8:319—321 (Letter).
35. Lind L, Lundstrom A, Hofer PA, Holmgren G. The gene for diffuse palmoplantar keratoderma of the type found in northern Sweden is localized to chromosome 12q11-q13. Hum Mol Genet 1994; 3:1789–1793.
36. Maillefer RH, Greydanus MP. To B or not to B: is tylosis B truly benign? Am J Gastroenterol 1999; 94:829–834.
37. Clarke CA, Howel-Evans W, McConnell RB, Sheppard PM. Carcinoma of oesophagus in assocation with tylosis. Br Med J 1959; 2:1100.
38. Ahsan H, Neugut AI. Radiation Therapy for Breast Cancer and Increased Risk for Esophageal Carcinoma. Ann Intern Med 1998; 128:114–117.
39. Scully C, el-Kom M. Lichen planus: review and update on pathogenesis. J Oral Pathol 1985; 14:431–458.
40. Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. Ann Intern Med 1995; 123:615–620.
41. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. J Am Acad Dermatol 2002; 46:207–214.
42. Calabrese C, Fabbri A, Marco B, et al. Squamous cell carcinoma arising in esophageal lichen planus. Gastrointest Endosc 2003; 57:596–599.
43. Jacobson BC, Hirota W, Baron TH, Leighton JA, Faigel DO. The role of endoscopy in the assessment and treatment of esophageal cancer. Gastrointest Endosc 2003; 57:817–822.
44. Winawer S, Sherlock P, Belladonna J, Melamed M, Beattie E. Endoscopic brush cytology in esophageal cancer. JAMA 1975; 232:1358.
45. Zargar S, Khuroo M, Jan G, Mahajan R, Shah P. Prospective comparison of the value of brushings before and after biopsy in the endoscopic diagnosis of gastroesophageal malignancy. Acta Cytol 1991; 35:549–552.