Report of the Barrett's Esophagus Working Group

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Report prepared by:
Kate Z. Guyton PhD, *CCS Associates*
Ellen Richmond MS, *NCI, Division of Cancer Prevention*
Ernest T. Hawk MD MPH, *NCI, Division of Cancer Prevention*

We the undersigned members of the Barrett's Esophagus Working Group concur with the enclosed report.

Marcia Canto, MD, MHS	Dawn Provenzale, MD, MS
Donald Castell, MD	Brian Reid, MD, PhD
Glenn Eisen, MD, MPH	Richard Sampliner, MD
Arlene Forastiere, MD	Prateek Sharma, MD
Raj Goyal, MD	Jon Stuart Spechler, MD
Charles Lightdale, MD	Jacques Van Dam, MD, PhD
Stephen Meltzer, MD	Thomas Vaughan, MD, MPH
Stephen Piantadosi, MD, PhD	Kenneth K. Wang, MD

EXECUTIVE SUMMARY

I. Background

Incidence rates for adenocarcinoma of the esophagus have risen dramatically in the US during recent decades. Among white males, the annual rates per 100,000 rose from 0.7 in 1974–1976 to 3.2 in 1992–1994, an increase of 350% [1]. The incidence of esophageal adenocarcinoma is increasing more rapidly than that of any other cancer in the US [2]. Although adenocarcinoma represented < 8% of esophageal cancers 30 years ago, it is now the dominant form among white males (60%) [2] and may thus represent the majority of the 13,200 new cases and 12,500 deaths of esophageal cancer estimated for 2001 in the US [3]. The prognosis for esophageal adenocarcinoma is indeed poor; five-year survival is estimated at 17%, median survival is only 15 months, and nearly all patients eventually die due to this disease [4, 5].

The only known premalignant condition for esophageal adenocarcinoma is Barrett's Esophagus (BE). The risk of adenocarcinoma in BE patients has been estimated at 30–125 times that of age-matched controls (reviewed in [6]); cancer risk is especially high in those with high grade dysplasia. Symptomatic gastroesophageal reflux disease (GERD) is a known risk factor for both BE and esophageal adenocarcinoma. The estimated prevalence of BE in GERD patients is 6–12% (reviewed in [7]). GERD is a common condition, and up to 20% of the US adult population reports symptoms associated with chronic heartburn [8]. Based on these findings, BE is estimated to affect more than 700,000 adults in the US [7].

These data support the continued development of a national research agenda to establish the etiology of GERD, BE, and esophageal adenocarcinoma, and to develop strategies to address the current and increasing public health impact. To advance this agenda, National Cancer Institute (NCI) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened an expert panel of NIH staff and extramural scientists to: 1) examine each institute's current research portfolios related to GERD, BE, and esophageal adenocarcinoma; 2) review the current state of the science in BE-related carcinogenesis, screening, prevention, and treatment; and 3) propose a national research agenda that will fill gaps in the current knowledge base and identify opportunities to stimulate necessary research.

II. Process and Organization of the BEWG

A. Review of Current Research Portfolios

The NCI and NIDDK recent research portfolios relevant to GERD, BE, and esophageal cancer are summarized below.

NIDDK has supported research on reflux disease and BE since 1995. In 1994, concern over the rising incidence of adenocarcinoma prompted NIDDK leadership to meet with BE investigators. Thereafter, in 1995, NIDDK issued its first program announcement that included reflux disease as well as BE. Planning grants for reflux disease therapeutics and dyspepsia were awarded beginning in 1996. In 1998, this program announcement was reissued and more BE-specific grants were received. Also in

1998, NIDDK and the Veterans Administration convened a joint meeting to develop evidence-based recommendations for screening, surveillance, and treatment of BE and reflux disease. Identified research gaps included the epidemiology and natural history of BE, as well as the need for controlled trials to assess the potential benefit of antireflux surgery and ablative therapy. The current NIDDK portfolio for research in reflux disease and Barrett's provides approximately $1,000,000 in direct costs from all funding mechanisms. This portfolio includes an SBIR grant, a K08 national career development award, a K24 mentor career development award, and an R03 which together total $400,000. Three R01 grants (totaling $650,000 of the >$171,000,000 provided through 530 NIDDK R01 awards), specifically support research in reflux disease.

The NCI portfolio on esophageal neoplasia includes 24 unique grants and contracts with ≥20% relevance to esophageal carcinoma - amounting to approximately $24,000,000 in disbursements through 1999 (based on the NCI/Office of Science Planning database). A larger group of projects (e.g., Cancer Center Core Grants or Cooperative Group grants) may involve work in esophageal cancer, but are coded as having <20% relevance specifically to esophageal carcinoma. Of the 24 unique grants and contracts with clear relevance to esophageal cancer, 16 projects focused specifically on either BE or adenocarcinoma. These projects represented $17,000,000 of the > $5,000,000,000 in NCI extramural funding provided from 1997–1999. Projects on the biology and etiology of BE include studies of the role of p16, retinoid receptors, molecular changes, chromosomal instability, and environmental factors. Another project aimed to standardize the esophageal biopsy protocol as a foundation for future efforts. Research in screening and diagnosis has largely involved the development of optical biopsy methods, using either laser-induced fluorescence or light scattering spectroscopy; denaturing HPLC examination of genetic abnormalities in biopsies; and evaluation of molecular alterations within a tumor as a predictive measure of therapeutic efficacy. Prevention projects have focused on preclinical model and biomarker development. Clinical BE prevention trials include one study of a dietary intervention, and Phase II evaluations of the chemopreventive efficacy of the COX-2 selective inhibitor, celecoxib, and the ornithine decarboxylase inhibitor, difluoromethylornithine. Another clinical prevention trial is evaluating a novel probe for photodynamic therapy (PDT). A review of the PDQ database to complement the above portfolio analysis reveals several esophageal cancer treatment trials. These involve assessments of PET scanning for staging and response characterization, and quality of life instruments for outcomes analysis. In addition, novel therapeutics are being evaluated in five Phase I dose-finding and in twelve Phase II preliminary efficacy trials. Three large Phase III chemotherapeutic trials are also ongoing.

B. Meetings of the BEWG

Sixteen extramural experts on GERD, BE, and esophageal adenocarcinoma, together with NCI and NIDDK staff, participated in a series of meetings in February 2001 with the goal of developing recommendations for a national research agenda. Appendix A provides a complete listing of BEWG participants, all of whom reviewed this report. In each session, experts reviewed the current science and identified key opportunities and priorities for future research in BE. The meetings were organized around three primary issues in BE:

- *Epidemiology, Etiology, and Risk Factors*, meeting date February 5, 2001
- *Screening, Early Detection, Imaging, and Surveillance Guidelines*, meeting date February 16, 2001
- *Preventive and Therapeutic Interventions*, meeting date February 26, 2001.

The research priorities identified at each session are summarized below.

C. Research Priorities

– *BEWG Session I: Epidemiology, Etiology, and Risk Factors*

This first session reviewed the pathogenesis, prevalence, and incidence of GERD, BE metaplasia, dysplasia, and cancer. The molecular biology and biomarkers of progression and cancer risk in BE were also discussed. The following recommendations were proposed at Session I of the BEWG:

1. Determine the incidence and prevalence of BE and GERD in asymptomatic and symptomatic populations.
2. Develop standardized questionnaires using common data elements to identify etiologies and risk factors for BE (*e.g.* tobacco and alcohol use, lower esophageal sphincter (LES) medications, obesity, diet, GERD).
3. Investigate, develop and validate biomarkers of progression (individually and as panels) in BE.
4. Create a multicenter, multidisciplinary clinical infrastructure to facilitate risk assessment and intervention trials for BE.

– *BEWG Session II: Screening, Early Detection, Imaging, and Surveillance Guidelines*

The second BEWG session provided a review of current screening and surveillance guidelines for BE, including a discussion of the cost-effectiveness of surveillance, and approaches for improving the predictive performance of endoscopic screening and surveillance. Strategies for promoting data quality in population-based screening and surveillance were also addressed. Additionally, novel screening techniques and clinical imaging technologies were presented. The following recommendations, listed in order of priority, were proposed at Session II of the BEWG:

1. Establish a multicenter, multidisciplinary research network to facilitate cohort, screening, surveillance and intervention studies in BE.
2. Conduct a surveillance trial to establish the natural history and clinical management of BE.
3. Conduct a screening study in a broad-based population of asymptomatic and symptomatic patients to establish the incidence, prevalence, risk factors and etiology of GERD and BE.

– *BEWG Session III: Preventive and Therapeutic Interventions*

The final BEWG session included topics such as endoscopic treatments (particularly thermal ablation, mucosal resection and PDT), pharmacologic interventions (including GERD therapies and molecularly-targeted approaches), and dietary modification strategies for treating and preventing BE and BE-associated esophageal adenocarcinoma. Clinical trial design and statistical issues were also

reviewed. The following recommendations, listed in order of priority, were proposed at Session III of the BEWG:

1. Establish a multicenter, multidisciplinary collaborative network among experts in BE to facilitate screening, surveillance and intervention studies. This network would provide a shared infrastructure for central pathology, endpoint definition, data management, and the development of common data elements and standardized questionnaires.
2. Conduct a surveillance trial to establish the natural history and clinical management of BE.
3. Conduct an intervention trial to evaluate the efficacy of ablative, surgical and molecularly-targeted pharmacological strategies in BE.
4. Employ a minimally invasive technology to conduct a screening study in asymptomatic and symptomatic populations to establish the risk factors and etiology of BE.

III. Conclusions

The NCI and NIDDK research portfolios dedicated to research on GERD, BE, and esophageal adenocarcinoma should be substantially augmented. This recommendation is mandated by the recent dramatic, but poorly understood, increase in the incidence of esophageal adenocarcinoma, a disease that typically presents at an advanced stage when therapeutic options are limited, and outcomes correspondingly dismal. An additional stimulus is the accessibility of esophageal tissue, that permits serial, prospective analyses; indeed, this situation provides exceptional opportunities to establish risk factors, identify molecular determinants of neoplastic progression, and evaluate the risks and benefits of early interventions. Improved understanding of the genesis of this disease is critical to the development of molecularly-targeted preventive and therapeutic strategies, which offer the greatest chance for benefit while minimizing risks.

BE-associated carcinogenesis also provides an important model for carcinogenesis in less accessible organs. More than 90% of BE and esophageal adenocarcinomas harbor p16 and p53 mutations, which are among the most common genetic lesions in human cancers. Thus, in addition to providing significant benefit to BE patients, investment in esophageal cancer research is likely to have far-reaching implications for our understanding of cancer overall.

To realize the promise of research in this area, the BEWG recommends the establishment of a multicenter collaborative network of gastroenterologists, clinical epidemiologists, molecular/ cellular biologists, and other dedicated professionals. This multidisciplinary network would furnish a critically-needed infrastructure for basic and clinical research in BE, including patient registry, centralized pathology, biomarker development, tissue banking, centralized data management, common data elements and standardized questionnaires. This network would allow for efficient access to persons with GERD, BE, and adenocarcinoma and their at-risk tissues, thereby optimizing clinical investigations designed to identify, assess, and develop new technologies and strategies for screening, surveillance, and intervention. Such studies would further define risk factors, as well as the etiology and prevalence of GERD, BE, and esophageal adenocarcinoma. In addition, this effort would promote the

development of urgently-needed clinical management strategies as well as molecularly-targeted interventions. Timely implementation of this recommendation is imperative.

FULL REPORT OF THE BEWG

The full report of the BEWG provides a detailed summary of each scientific presentation, including the specific recommendations provided by each speaker. A bulleted summary of the discussion for each meeting is also included. A bibliography can be found in Appendix B.

BEWG Session I: Epidemiology, Etiology, and Risk Factors
Executive Plaza North, Conference Room J, February 5, 2001

RAJ GOYAL (Harvard University)
Pathologic Spectrum of Barrett's Esophagus

Between 1950 to 1990, the incidence of esophageal adenocarcinoma increased ten-fold from 0.1 to 1.0 per 100,000. However, accurate assessment of the incidence rate is compromised by the lack of standardized diagnostic criteria and of a national database to track esophageal adenocarcinoma and related conditions, including GERD and BE. The prevalence of BE rises after age 40 and peaks around age 70; therefore, as the US population ages, it is expected that BE will become an increasingly prominent medical condition requiring ever-expanding resources.

BE is the primary risk factor for esophageal adenocarcinoma and is characterized by metaplastic replacement of normal squamous epithelium in the lower esophagus with specialized columnar epithelium (SCE) unique to BE. Progression begins with esophagitis, caused in most cases by gastroesophageal reflux. Continual reflux may lead to GERD, a precondition of BE, characterized by scarring and formation of SCE. A common symptom of GERD is heartburn, although symptoms diminish during progression to BE; indeed, very few patients with esophageal adenocarcinoma report heartburn as a symptom. The diagnosis of BE generally refers to the presence above the gastroesophageal junction of $ 2–3 cm. SCE. The reported prevalence of BE ranges from 1–7%. However, fewer than 5% of cases may be detected, as is suggested by comparison of the clinically-diagnosed BE prevalence (22.6 per 100,000) to that in a prospective autopsy series (376 per 100,000) [9].

A standard BE definition should be widely adopted; the lack of such standardization to date has limited the ability to correlate data among BE studies and trials. Research should focus on evolution of specialized intestinal metaplasia in the columnar-lined esophagus that characterizes BE. Another priority is research to understand etiologic and other differences between short- and long-segment BE. It is particularly important to determine whether they bear the same risk for progression to cancer. Research is also needed to elucidate the role of acid reflux in the development of metaplasia, and the progression of metaplasia to BE and subsequently to adenocarcinoma. Endoscopic screening efforts should target patients with reflux symptoms to permit early intervention and to allow study of risk factors for progression. Asymptomatic patients should also be screened; of particular concern is the development of screening strategies to identify those at high risk (or who have prevalent cancer) who are symptom-free.

Recommendations:

1. BE definition
2. Evolution of specialized intestinal metaplasia
3. Short segment BE: Surveillance strategies
4. Acid reflux: Role in etiology
5. Challenges in screening/prevention
   - Reflux symptoms
   - Most cancers are prevalent

JAY EVERHART (NIDDK)
Epidemiology of Gastroesophageal Reflux Disease

The Clinical Outcomes Research Initiative (CORI) database includes results from nearly 50,000 endoscopies performed from 1998–2000 at more than 100 private, university, and VA participating sites. Indications for upper endoscopy included reflux (19%) and dysphagia (20.7%). Diagnoses after endoscopy included esophagitis (15.4%), suspected BE (4.9%) and suspected tumors (0.5%). Reflux and/or dysphagia were reported by 39 and 66% of patients diagnosed with suspected BE or esophagitis, respectively. The highest BE prevalence was among white men ages 50–70 (mean age 59.1).

The prevalence of esophagitis is rising at an alarming rate; hospitalizations for esophagitis increased four-fold between 1970 and 1990 in US veterans [10]. Esophagitis is also a precursor condition for BE. Possible risk factors for esophagitis include the following:

- Age. Esophagitis increases with age, as does BE, with most cases diagnosed at $ 40 years of age.

- Hiatal hernia. Hiatal hernia was found in 60–80% of patients with reflux esophagitis, but only 7–12% of endoscopic controls. In addition, the degree of reflux is associated with the size of the hiatal hernia. No prospective studies have adequately examined the temporal relationship between hiatal hernia and esophagitis. Other than obesity, risk factors for hiatal hernia are poorly defined.

- *Helicobacter pylori* (*H. pylori*). The third National Health and Nutrition Examination Survey (NHANES III) found that *H. pylori* prevalence increased with age in both men and women [11,12]. The overall incidence of *H. pylori* has dropped dramatically since 1900 [13]. *H. pylori*-related corpus gastritis, characterized by impaired acid secretion, may confer protection against esophagitis. Several population-based studies reported an inverse association for GERD and *H. pylori* infection [14–16]. *H. pylori* protection may involve a cytotoxin-associated gene product (CagA); in a recent endoscopic study, CagA was inversely related to reflux and BE [17].

- Overweight and obesity. Many recent controlled studies have reported an elevated risk of GERD

with increasing body mass index (BMI) [18–21]. Hospitalization with GERD also increases with increasing BMI.

- Family history and genetics. Romero found an odds ratios of 1.5 for reflux, 2.2 for BE, and 2.8 for adenocarcinoma in a small family study [22]. In a study of five families with severe pediatric GERD, Hu identified the 13-cM region of chromosome 13q as a possible area of linkage [23].

- Improved detection. Development of the flexible endoscope in the 1970s may have enhanced detection of esophagitis, GERD, BE and adenocarcinoma.

- Other factors. Other factors that may positively or negatively influence GERD development include central adiposity, viral infections other than *H. pylori*, drugs (*e.g.*, NSAIDs, anticholinergics, calcium channel blockers), cholecystectomy, diet (*e.g.*, fat intake, antioxidants), smoking, and childhood reflux disease.

Future studies should carefully define cases and select appropriate controls. Half the US population reports at least occasional GERD symptoms, but only a small fraction have endoscopic evaluations. Results of these endoscopic evaluations should be captured in a CORI-type or other national database. The esophagogastroduodenoscopy (EGD) is insensitive for mild GERD, which may be better detected by 24-hour pH monitoring. Improved collaboration among epidemiologists and gastroenterologists would facilitate the elucidation of risk factors and would ensure accurate diagnoses of symptomatic and asymptomatic individuals. Research priorities include exploring the association between overweight/obesity, particularly mechanical or paracrine central adiposity, and esophagitis. The role of hiatal hernia and *H. pylori* virulence in esophagitis, and the association of childhood reflux with subsequent adult disease should also be investigated. Finally, family studies should employ emerging molecular research tools to define the genetic factors associated with each stage in the progression from esophagitis to adenocarcinoma.

Recommendations:

1. Case definition (controls)
2. Endoscopic database: CORI *versus* National
3. Collaborations
4. *H. pylori* virulence factors
5. Overweight/central adiposity
6. Hiatal hernia
7. Childhood reflux follow-up
8. Family studies: susceptibility

PRATEEK SHARMA (University of Kansas)
Prevalence and Incidence of Barrett's Metaplasia, Dysplasia, and Cancer

BE is defined as columnar-appearing mucosa on EGD that is histologically confirmed to be intestinal metaplasia. There are great disparities in the reported prevalence for BE. For example, a BE prevalence of 1.7% was reported in 30,000 patients, with and without GERD, who had EGD [24]. Subsequent studies found prevalence rates of 3–15% [25–28]. The prevalence of BE in GERD is estimated at 4–7% [29,30,31]; of 178 over-the-counter antacid users who underwent endoscopy, 6% were diagnosed with BE and one patient had adenocarcinoma [32]. Only one of 20 BE cases may be detected, as is evidenced by comparison of the clinically-diagnosed BE prevalence (22.6 per 100,000) to that in a prospective autopsy series (376 per 100,000) [9]. Increased detection may be a factor in the dramatic rise in BE prevalence from 1965–1985; during this period, comparable rates of increase were found for both BE prevalence and the number of EGDs performed [9].

More than half of BE cases are < 3 cm, defined as short-segment BE (SSBE); $ 3 cm of BE is defined as long-segment BE (LSBE). SSBE prevalence increased more than 4-fold from 1985–1996, during which time the number of EGDs performed remained constant. SSBE and LSBE have similar demographics; each increases with age, and is more common in white males [27,28,33,34]. SSBE and LSBE share the same pathogenesis, appearing to represent different stages of the same disease continuum, and are managed in a comparable manner. Surveillance is recommended for SSBE as well as LSBE, because of associated cancer risk [35]. Dysplasia incidence in SSBE is estimated at about 6% [9,36,37]. Adenocarcinoma incidence in BE patients ranges from 0.4–1.9% per year [34,38–42]. Cancer incidence in SSBE is approximately 0.4% per year [34,35,43]. Increased cancer risk is associated with LSBE; cancer incidence is 0.6% for 3–6 cm, increasing to 1.8% for 10 cm BE [43]. Limitations of studies evaluating adenocarcinoma risk in BE include lack of consistency in the BE definition, lack of distinction between cancer prevalence and incidence, short follow-up, and referral bias. Shaheen noted a possible publication bias in the reporting of cancer risk in BE, favoring small studies that show a positive link [44].

The Barrett's Esophagus Study Trial (BEST) was a multicenter clinical and outcomes project with a single large database of BE patients. The BEST study used standardized protocols and definitions to investigate demographic factors, BE length, dysplasia (high- or low-grade) and adenocarcinoma in 1376 BE patients. Preliminary results gave prevalence rates of 6.7%, 3%, and 7.3% for adenocarcinoma, high-grade dysplasia, and low-grade dysplasia, respectively. Twelve incident cancers were noted during 2546 patient-years of follow-up; the mean time to incidence of cancer was 5.3 years, and the incidence was 0.5% per year. The incidence of high-grade dysplasia was 0.9% per year and the mean time to incidence was 3.0 years. Future efforts will seek to evaluate potential risk factors for progression such as demographics (age, gender, ethnicity), GERD duration and frequency, BE length, hiatal hernia, *H. pylori* infection, alcohol/tobacco use, medications (aspirin, NSAIDs, PPIs), anti-reflux surgery, and BMI.

In summary, the true prevalence of BE is not known. Prevalence is estimated at . 10% in GERD patients, and at . 1% in patients undergoing endoscopy. The prevalence of SSBE exceeds that of

LSBE. BE appears to largely be a disease of white males, with mean time of incidence . 60 years of age. Although the exact incidence of cancer in BE is unknown, it is . 0.5% per year. Thus, relatively few patients develop BE from GERD, and fewer still progress from BE to dysplasia or cancer. Future priorities include accurately defining the cancer incidence in a large cohort, comparing SSBE *versus* LSBE, and identifying risk factors (demographic, endoscopic, biomarker, *etc.*) for progression from BE to dysplasia and cancer.

Recommendations:

1. Define dysplasia/cancer incidence in large cohort of BE patients
2. Comparative study of SSBE *versus* LSBE
3. Identify risk factors for progression:
   - Demographic
   - Endoscopic
   - Biomarker

THOMAS VAUGHAN (University of Washington)
Etiology and Epidemiology of Barrett's Esophagus: Opportunities for Prevention

A rapid rise in esophageal adenocarcinoma incidence has been observed in the US, New Zealand, and Europe. Although esophageal adenocarcinoma is most common in US white men, the incidence of the disease has also increased among women and African Americans in the US. Esophageal adenocarcinoma incidence increased from 1995–1998 by 5.7% in white men, and by 9% in all whites. Histologic progression to cancer entails the sequential development of chronic GERD (in 6–12% of normal individuals), BE metaplasia (in 10% of GERD patients), high-grade dysplasia and finally adenocarcinoma (at a rate of 0.5–1.0% per year in BE patients). The rapid rise in incidence suggests a major role for environmental factors in this process. In support of this view, little evidence of familial aggregation was found for BE [45]; also, no differences were noted in susceptibility based on biotransformation enzyme polymorphisms (*e.g.* GST, CYP, NAT).

Small prospective and community-based case-control studies suggest that risk is enhanced by factors that either increase reflux (*e.g.*, tobacco and alcohol, dietary fat, chocolate, caffeine, obesity, medications) or are genotoxic (*e.g.*, a diet low in vegetables and fruits, tobacco, dietary nitrites and nitrosamines). Several of these factors appear to differentially affect the risk of esophageal squamous cell carcinoma and adenocarcinoma. In a case-control study, tobacco use increased risk of esophageal squamous cell carcinoma five- and eight-fold in current and heavy smokers, respectively; risk rapidly decreased with cessation. In contrast, the two- to three-fold elevations in esophageal adenocarcinoma risk in smokers did not decline upon cessation [46–48]. Preliminary results of a separate case-control study found odds ratios for increased risk of GERD and metaplasia of 1.7 and 2.4, respectively, for current *versus* never smokers. Alcohol use increased esophageal squamous cancer risk five- to seven-fold, but was not associated with esophageal adenocarcinoma risk; the latter was slightly

increased by hard liquor consumption and slightly decreased by wine consumption.

Dietary factors also appear to affect esophageal adenocarcinoma risk. Relative risks (estimated from highest *versus* lowest quartile comparisons) were as follows: total fat, 2.2; saturated fat, 2.3; percent of energy from fat, 1.6; fat (not otherwise specified), 1.6 and 2.9 [49,50]. Reduced relative risks were found for the following: noncitrus fruit, 0.6; dark green vegetables; 0.6; lutein, 0.5; vegetables, 0.2; vitamin C, 0.1; salad vegetables, 0.3; fruit, 0.2; cruciferous vegetables, 0.3; fiber, 0.2–0.6 [49–53]. Increased body weight has also been associated with increased risk of esophageal adenocarcinoma (three- to eight-fold) and of BE metaplasia (odds ratio, 2.4) [54,55]. Approximately 85% of men and about 80% of women BE patients have BMIs greater then 25 kg/m^2. Preliminary findings suggest that increased waist:hip ratio elevates the risk of aneuploidy (odds ratio, 4.3) and of BE metaplasia (odds ratio, 2.0).

Medications that relax the LES may also increase esophageal adenocarcinoma risk. LES-relaxing drugs include beta agonists (for asthma), calcium channel blockers (for hypertension), tricyclic antidepressants, and anticholinergics. A Swedish study found an increased esophageal adenocarcinoma risk for LES-relaxing drugs (odds ratio, 3.8) [56]; a US study described similar findings for beta agonists (odds ratio, 1.7–2.3) and theophylline (2.5–3.1) [57].

Opportunities for prevention of esophageal adenocarcinoma include lifestyle modifications emphasizing tobacco cessation, improvements in diet, and weight loss. Another alternative is chemoprevention with NSAIDs, selenium, and other micronutrients (*e.g.*, vitamin E, folate). NSAIDs reduce inflammation, cellular proliferation, and oxidative damage to cells and promote apoptosis, all effects that could benefit BE patients. Reduced risk for aneuploidy in BE patients was observed in current (odds ratio, 0.6) or ever (odds ratio, 0.5) NSAID use. Clark found that selenium reduced esophageal cancer risk (relative risk of 0.30) [58]; however, the results lacked statistical significance due to the small number of cases. Preliminary results suggest that low serum selenium is associated with increased risk of high-grade dysplasia and increased tetraploidy in BE patients.

Future research is needed in the following areas:

1. Anthropomorphic measures:
   - Determine whether BMI or waist:hip ratio is the more significant risk factor.
   - Assess stages of progression at which these measures are relevant.
   - Determine if waist:hip ratios explain gender differences in incidence.

2. Diet: Replicate case-control studies with prospective design. Of particular concern is that control participants in case-control studies are more likely to have healthier lifestyles than the overall population, and that recall of diet is error-prone and can be biased by disease history. Research questions include the following:
   - Why does fat intake increase risk– because of increased BMI/waist:hip ratio, increased reflux, or a hormonal mechanism?

- Do effects differ by types of fat?
- At which stage is fat intake important?
- Are certain vegetables (*e.g.*, crucifers) more strongly associated with reduced risk?
- What are the molecular targets of dietary nutrients (*e.g.*, GST upregulation)?
- Are there interactions between antioxidants and dietary carcinogens (*e.g.*, vitamin C and nitrites, vitamin E and smoking)?

3. LES medications: Replication of findings is needed. To what extent is increased esophageal adenocarcinoma risk driven by asthma medications (or asthma itself)?

4. Chemoprevention: The suggestion of decreased risk for NSAID and selenium intake should be replicated in observational studies and clinical trials. Important questions include:
   - What stage(s) of the disease (*i.e.*, metaplasia, dysplasia, adenocarcinoma) are likely to be the target of effective interventions?
   - What are the underlying molecular mechanisms?
   - Would patients have differing susceptibilities for benefit from these agents?

5. Validated intermediate markers: Needed for both observational and intervention studies. Development of intermediate markers would reduce time needed to adequately assess interventions, number of patients needed for studies, and follow-up intervals. Research on intermediate markers will also enhance understanding of the disease process and biologic pathways amenable to intervention.

6. Screening and surveillance: Employ screening to identify high-risk groups for subsequent surveillance/intervention. Critical questions for screening include:
   - Who among the 10% of the US population with reflux symptoms is at high-risk for BE?
   - Do asthmatics have an increased risk for BE and cancer, and should this group be targeted?
   - What strategies could be employed to identify the 40% of prevalent adenocarcinoma cases that do not report reflux symptoms?

Recommendations:

1. Anthropomorphic measures
   - Are BMI or waist:hip measures more important?
   - When do they matter?
   - Can they explain gender differences?
2. Diet
   - Replicate case-control data
   - Fat
   - Fruits/vegetables
   - LES medications: Replicate findings
3. Chemoprevention (*e.g.*, NSAIDs/selenium)

- Can preliminary findings be replicated?
- When do they matter?
- Mechanisms of action?

4. Intermediate markers: Risk
5. High-risk cohort identification
   - Reflux
   - Asthmatics
   - Asymptomatic prevalent esophageal adenocarcinomas

DONALD CASTELL (Medical College of Pennsylvania)
Gastroesophageal Reflux as an Etiologic Factor in Barrett's Esophagus

Controversy regarding the etiology of BE stems from 1950, when Barrett first described the condition as a congenital short esophagus [59]. In 1953, Allison and Johnstone supported the congenital etiology but suggested that BE might be acquired in some cases [60]. Haywood in 1961 proposed that BE could be acquired by upward migration of the gastroesophageal (GE) junction epithelium [61]. In 1970, Bremmer further defined this upward migration as a "creeping substitution" of columnar epithelium caused by acid injury [62]. Bremmer's hypothesis that BE is an acquired condition secondary to chronic gastroesophageal reflux is now widely accepted. BE is diagnosed in 10–15% of GERD patients, and is related to the duration of symptoms and age of the patient. In many BE patients, symptoms (*e.g.*, heartburn) actually decrease in severity and frequency as normal epithelium is replaced by columnar epithelium, which is less sensitive to acid reflux [63–65].

BE is treated with proton pump inhibitors (PPIs), which are effective for alleviating GERD symptoms, but may not completely abolish acid production [66]. Pulsed acid exposure enhanced cell proliferation in *ex vivo* organ cell cultures of endoscopic BE biopsies; this proliferative effect was not seen at normal pH, with continuous acid exposure, or in cells isolated from the duodenum or normal esophagus [67]. This finding is in keeping with the observation that, although PPIs appear to regress BE [68], residual BE islands were found in BE patients treated long-term with lansoprazole [69]. Supplementation of PPI treatment with the histamine-receptor antagonist ranitidine effectively controls acid reflux; nonetheless, squamous islands were found in five of nine patients treated with either PPI bid (two patients) or PPI bid plus ranitidine (seven patients). It is thus not known whether effective acid reduction can completely regress BE, or if dysplasia or cancer development is affected by PPIs.

In summary, acid exposure caused by esophageal and LES motility underlies BE development. The acid exposure stimulates columnar replacement of injured squamous mucosa, which in turn shows decreased sensitivity to refluxed acid. Research is needed to more clearly define patients at risk for GERD and BE. More accurate and effective screening and detection modalities should be explored and evaluated in clinical trials. The level of acid suppression providing optimal therapy remains controversial. In particular, the role of acid control at each stage of disease progression from GERD to BE to cancer

should be explored.

Recommendations:
1. Refine population at risk
2. Early detection: Emphasize screening
3. Role of acid control: Adequacy

STEPHEN MELTZER (University of Maryland)
Molecular Genesis of Barrett's Neoplasia

The development of BE-associated adenocarcinoma appears to entail genomic instability (aneuploidy and chromosomal alterations), tumor suppressor gene inactivation (by LOH, point mutation, and promoter hypermethylation), and altered expression of key genes (*e.g.*, COX-2). Advances in the molecular characterization of BE have been achieved with translational research (*e.g.*, examining plasma biomarkers), new technologies (*e.g.*, cDNA microarrays) and the appropriate application of bioinformatics. BE metaplasia is a disorder of clonal proliferation during which clonal fields of abnormal cells populate the metaplastic, dysplastic, or cancerous epithelium. Each field has a unique DNA content (diploid or aneuploid). Each field also contains specific DNA alterations, including unique mutations, deletions, and altered methylation. Multiple sites of LOH have been identified in BE-associated adenocarcinoma, including 17p (p53 locus), 5q (adenomatous polyposis coli (APC) locus), 13q (retinoblastoma (Rb) locus), 18q (DCC and SMAD4 loci), 17q (TCF-2 locus), and 9p (p16/p15 locus). Ninety percent of BE-associated adenocarcinomas carry mutations in the p53 gene, which encodes a nuclear DNA-binding protein that activates gene transcription. Wild-type p53 causes cell-cycle arrest of DNA-damaged cells, allowing time for DNA repair. Thus, p53 is referred to as a "gatekeeper" gene. A unique spectrum of p53 mutations is seen in BE, with frequent nonsense mutations. p53 mutation appears to be an early event, and is common in nondysplastic BE. p53 mutation may be a marker of progression risk; 30%, 15% and 0% of cancer, BE, and control patients, respectively, showed evidence of p53 mutations.

DNA promoter hypermethylation is associated with silencing of gene expression. Almost half of tumor suppressor genes mutated in familial cancer syndromes show hypermethylation in sporadic tumors; hypermethylation most commonly occurs on cytosines in the sequence 5'-CpG-3'. p16, a cyclin-dependent kinase inhibitor, was hypermethylated in 38% of esophageal tumors (8 of 21 patients), with an inactivation rate of 73% [70,71]. Point mutations in p16 are seen in 10% of esophageal tumors. Of interest is the use of hypermethylated DNA in plasma as a biomarker for risk of BE and subsequent adenocarcinoma; however, the presence of hypermethylated DNA in plasma may indicate a more aggressive tumor. Hypermethylated APC was found in the plasma of 25% of esophageal adenocarcinoma patients, and high plasma levels were significantly associated with reduced patient survival; unfortunately, this marker was not found in the plasma of BE patients [72].

Cyclooxygenase-2 (COX-2) is upregulated in gastrointestinal cancers and precancerous lesions (*e.g.*, colonic adenomas). Elevated COX-2 mRNA and protein was found in 80% of BE tissue samples (17 of 20 patients); this increase was found in tissues from all five adenocarcinoma patients studied [73]. COX-2 antagonism inhibits formation and causes regression of colon polyps, and may also prove a useful strategy for prevention of BE and adenocarcinoma.

cDNA microarrays can simultaneously characterize the expression of thousands of genes. Hierarchical clustering is a statistical method of identifying characteristic patterns of gene expression among groups of lesions or patients. "Clustergrams" representing the intensity of expression of many genes were used to identify patterns characteristic of BE and adenocarcinoma. Cluster analysis could distinguish BE from esophageal cancer specimens. Within the cancer group, two squamous cancers, one signet ring cancer and three adenocarcinomas clustered separately. Artificial neural networks (ANNs) have also been applied as a diagnostic tool. ANNs are more powerful, accurate, and informative than hierarchical clustering, and have the potential to identify gene(s) or gene relationships important in determining phenotype. ANNs are programmed to identify specific characteristics of tumors (*e.g.*, histologic, chemical, physical) and make diagnoses based on data input. ANN was shown to be comparable, particularly in phenotypic identification, to radiologic examination of mammography results.

A major priority for future efforts is to develop biomarkers, especially plasma biomarkers associated with disease progression and recurrence. Genomic and bioinformatic approaches should be applied to molecular discovery in BE and adenocarcinoma. Biomarker development and validation should be an integral part of correlative studies to assess the benefits of prevention and early detection of BE. Increased screening of patients at high risk for BE and adenocarcinoma is also a priority. Multicenter studies with national databases are needed to provide strong, prospective, epidemiologic data on all aspects of BE and adenocarcinoma. National standards and common protocols, with standardized definitions for histologic, genetic, and clinical outcomes, are also required.

Recommendations:

1. Plasma biomarkers, especially for recurrence
2. BE meta/dysplasia molecular studies: Genomics/bioinformatics approaches
3. Biomarker development/validation: Correlative studies with prevention and detection
4. Increased screening
5. Multicenter studies

BRIAN REID (University of Washington)
Biomarkers of Barrett's Progression and Cancer Risk

Neoplastic progression of BE occurs through clonal expansion; understanding this progression will rely on identification of biomarkers for each stage of the disease. Approximately 2–8% of patients with low-grade dysplasia progress to cancer while 75% regress; among patients with high-grade dysplasia,

15% progress to cancer and 37% regress [74,75]. Current diagnostic approaches cannot distinguish those high-risk patients more likely to progress to cancer.

p16 abnormalities are associated with progression of BE. No patients with p16 (+/+) wild type and p16 (+/-) heterozygous genotypes progressed to adenocarcinoma, as compared with 20% of patients with the p16 (-/-) null genotype. Cyclin D expression was also associated with increased risk of BE progression. The p53 gene is commonly mutated in BE and esophageal adenocarcinoma, and 17p LOH is strongly correlated with progression from low-grade to high-grade dysplasia to cancer. p53 mutations are found in 40% of patients with low-grade dysplasia, 50% of patients with high-grade dysplasia and 69–92% of adenocarcinoma patients. 17p LOH is seen in approximately 9%, 57% and 80–100% respectively, of these same patients. Overall, 17p LOH appears to increase the risk of adenocarcinoma in BE patients by 16-fold, after approximately 5 years.

The use of flow cytometry to predict disease progression in patients free of dysplasia is of particular interest in the study of BE. A small study with 13-year follow-up reported that patients with aneuploidy had almost a 50% risk of progressing to cancer, whereas patients with diploid cells did not progress to cancer. In addition, comparison of histologic evidence to ploidy status indicated almost complete concurrence [76].

Loss of APC by hypermethylation of the promoter region occurred in abnormal esophageal tissue in 92% of 52 patients with esophageal adenocarcinoma and in about 40% of 43 patients with BE, but not in matching normal esophageal tissues [72]. Hypermethylated APC was found in the plasma of 25% of esophageal adenocarcinoma patients, and high plasma levels were significantly associated with reduced patient survival. Unfortunately, this marker was not found in the plasma of BE patients. Also, LOH on 17p, 9p, 18q, 5q, or 13q has been observed in the majority of patients prior to cancer diagnosis. Such information is instructive for development of biomarkers that indicate progression.

Telomerase expression also holds promise as a biomarker for disease, although it may principally serve as a late biomarker (*e.g.*, during high-grade dysplasia). Other potential biomarkers include the microfilament capping protein villin, which is highly expressed in BE and adenocarcinoma. However, preliminary studies indicate that its expression may be nonspecific for BE. Biomarkers of cell cycle control are also of interest.

Future efforts will require multidisciplinary, multisite approaches. Research is needed to definitively establish the molecular basis for the observed link between environmental factors and genetic disease. Longitudinal study of the natural history of BE is also of priority. Such studies should employ standardized biopsy protocols and a common database to collect and analyze results. Study findings need to be rapidly translated back to the medical community and the public.

Recommendations:

1. Multisite/multidisciplinary need

2. Link environment to genetic disease
3. Longitudinal natural history
4. Translation back to community

GROUP DISCUSSION AND RECOMMENDATIONS
Discussion Leaders: James Everhart and Sandra Melnick

The following issues were discussed:

1. Progression of BE
   - Biomarkers/intermediate markers
     – Rate of accumulation
     – Modulation
   - Longitudinal studies: Multicenter, multidisciplinary
     – Bioinformatics
     – Modeling
     – Imaging
   - Interest in shared protocols: Biological relevance of animal models (rat, dog)

2. Etiology/risk factors
   - Standard questionnaires
     – Tobacco
     – Alcohol
     – LES drugs
     – Obesity
   - Common data elements
     – Diet history
     – Reflux
   - Specimen repositories
   - Integrating environmental factors with biomarker data
   - Identifying high-risk population
     – *H. pylori*
     – Bile *versus* acid
     – Hormonal = gender
     – Childhood reflux
     – Hiatal hernia
   - Special populations that develop BE (*e.g.*, mentally disabled)
   - National initiative
     – GI/oncology cooperatives
     – HMO groups

3. Definition issues/cancer detection
    - Size of problem: Asymptomatic population
      – GUIACT FOB
      – NHANES
      – Over-the-counter antacid buyers
    - GERD definition
    - National meetings
    - Histologic agreement
    - Sampling protocol
    - Screening high-risk groups: Screening centers

Recommendations:

1. Determine the incidence and prevalence of BE and GERD in asymptomatic and symptomatic populations.
2. Develop standardized questionnaires using common data elements to identify etiologies and risk factors for BE (*e.g.*, tobacco and alcohol use, lower esophageal sphincter (LES) medications, obesity, diet, GERD).
3. Investigate, develop and validate biomarkers of progression (individually and as panels) in BE.
4. Create a multicenter, multidisciplinary clinical infrastructure to facilitate risk assessment and intervention trials for BE.

BEWG Session II: Screening, Early Detection, Imaging And Surveillance Guidelines
February 16, 2001

RICHARD SAMPLINER, University of Arizona
Current Screening and Surveillance Guidelines

BE is defined as a columnar-appearing area of the esophagus on endoscopy that is histologically confirmed to be intestinal metaplasia. The rationale for screening in BE is the observed rise in esophageal adenocarcinoma incidence in white males from the mid-1970s to the mid-1990s, amounting to a 350% increase [1]. Nevertheless, the incidence remains lower than that of squamous cell carcinoma in black males. BE is the only premalignant lesion known for adenocarcinoma of the esophagus and early detection may offer an opportunity to improve survival. Lagergren's population-based study in Sweden established recurrent reflux as a risk factor of adenocarcinoma of the esophagus; the odds ratio of patients with weekly reflux was nearly eight-fold [77]. Frequency, severity and duration of reflux were also independent risk factors. In the US, Lieberman also found that duration of GERD symptoms was a risk factor for reported (not biopsy-documented) BE [63]. However, BE patients experience decreased acid sensitivity and up to 80% of GERD patients do not seek medical attention [8]. Screening in BE is also limited by the current invasiveness and cost, estimated at $24,700 per life-year saved [78].

Three retrospective series have shown significant increase in five-year survival in BE patients undergoing endoscopic surveillance [79–81]. However, other factors that influence the suitability of a patient for surveillance include the risks of cancer, of surveillance itself, of intervention, and of other major co-morbidity. The interval for surveillance has also not been defined. It is assumed that a one-time look is sufficient if BE is not found, although supporting data are lacking. Published guidelines call for a 3-year surveillance interval if no dysplasia is found on two EGDs, or a yearly interval if low-grade dysplasia is confirmed; high-grade dysplasia should stimulate intervention [6]. The University of Washington protocol (jumbo four-quadrant biopsies every centimeter) may be particularly appropriate for high-grade dysplasia despite the labor and time required. Confirmation of dysplasia grade by an expert GI pathologist is also essential. Practice variability was found in two independent surveys of US endoscopists [82,83]. Most survey BE more frequently than every three years in the absence of dysplasia, and few use large-capacity biopsy forceps. Surprisingly, endoscopic ablation therapy for dysplasia is practiced by 25% of endoscopists. Most recommend esophagectomy for high-grade dysplasia despite that limited data are available on the natural history or cancer risk of dysplasia, survival without surgery. The mean ages of BE recognition and cancer development are 60 and 63, respectively. Many BE patients are elderly, have major co-morbidities, and are unfit candidates for surgery. At hospitals with a case volume less than six, the operative mortality of esophagectomy is 17.5%; most patients have esophagectomy performed at such low-volume hospitals. Four series in high-volume centers showed that 16–27% of resected cancers are early stage and have correspondingly good five-year survival rates [81,84–86].

Sources of variability in published studies of high-grade dysplasia include whether lesions are visible at endoscopy; lack of rigor in pre-operative surveillance endoscopy protocols; lack of definition of surgical specimen sampling; and changes in the cohort over time. Limitations of available data include inadequacies in patient number, length of follow-up, and endpoints. Additionally, very few women have been included in published series. The greatest unknown is whether the incidence and the risk for cancer development are stable over time. In a total of 708 patients from five series with a mean follow-up of 2.9–4.2 years, few without dysplasia or with low-grade dysplasia develop adenocarcinoma, whereas a clear cancer risk is evident for high-grade dysplasia. Sontag followed about 70 patients with high-grade dysplasia over 19 years and found that 15% went on to cancer [87]. In contrast, 54% of all patients at the University of Washington with high-grade dysplasia (including referrals) developed cancer within five years, compared with only 31% of patients whose diagnosis of high-grade dysplasia was made at the center. Thus, the published literature may overestimate the cancer risk of high-grade dysplasia.

Future efforts should seek to develop evidence-based criteria for screening and surveillance. BE screening criteria that are not well defined include the duration and severity of GERD symptoms, the age when screening should start and stop, and whether gender and ethnicity should be considered. BE is thought to be a 2-to-1, male-to-female disease even in asymptomatic populations. In the CORI database of 50,000 upper endoscopies of GERD patients, probable BE was found in 6% of white, but only 2% of African or Asian, Americans. Targeting surveillance to those at highest risk would provide the greatest benefit while reducing overall costs. Thus, risk stratification is essential; the development and validation of risk biomarkers is of priority. A critical issue is when should surveillance be stopped. Although there are no data, perhaps in a patient without dysplasia, who is 80 or older, and for whom death prior to esophageal cancer is likely. The Barrett's Esophagus Study Trial (BEST) multicenter trial will provide data on risk factors, prevalence and incidence that may clarify these issues.

Recommendations:

1. Define criteria for screening: Age, duration, gender, ethnicity
2. Risk-stratify for surveillance: Reduce overall costs by focusing on patients most likely to develop cancer
3. Biomarker validation: Employ in risk stratification

DAWN PROVENZALE, Duke University
Cost-Effectiveness of Surveillance in Barrett's

The cancer risk of BE patients has been estimated at 30–125 times that of an age-matched population, with the greatest risk in patients with high-grade dysplasia. Current recommendations for BE patients with dysplasia include endoscopic surveillance every 2–3 years. Most recommend esophagectomy for high-grade dysplasia, but because of the associated morbidity and mortality, others reserve surgery for cancer. The incidence of cancer in BE patients is largely unknown, with reports ranging from 0.2–2.1%

annually (or one in 48–441 patient years). Recent prospective endoscopic series suggest a cancer incidence of 0.4–0.5% annually (one in 208–251 patient years).

Is the surveillance of BE patients cost-effective compared to other common medical practices? Because no controlled trials have examined this issue, a computer cohort simulation was developed of 55-year-old patients with BE and no evidence of dysplasia by biopsy. This cohort is followed by endoscopy until death from esophageal cancer or competing causes. The model compared surveillance every one to five years to no surveillance (in which endoscopy was performed only for new or worsened dysphagia). Esophagectomy was indicated for high-grade dysplasia. Important parameters include a risk of endoscopy of 1.3 per 1000 procedures, and an incidence of cancer of 1.4 % (one in 227 patient years). An adjustment was made for quality of life after esophagectomy, which was estimated using the time trade-off technique as 0.97 out of 1.0. The costs included in the model were the actual direct medical costs from Duke University. The outcome measure, or the criterion for analysis, was the incremental cost-utility ratio [88]. This ratio is defined as the change in cost divided by the change in quality-adjusted life expectancy to move from a strategy of no surveillance to surveillance, or to move from less to more frequent surveillance intervals. The ratio is reported as dollars per quality-adjusted life year gained. The common technique of discounting was employed, at an annual discount rate of 5%.

The results indicate that no surveillance costs approximately $3000 and provides an additional 12.6 quality-adjusted life years (QALY). Surveillance every five years costs about $12,000 and provides 12.74 additional QALY, yielding an incremental cost-utility ratio of $98,000 per QALY gained. Strategies of surveillance every four, three, two and one year were found to be inferior to surveillance every five years because they cost more and yield a lower life expectancy due to the greater number of endoscopies, endoscopic complications and surgeries. The incremental cost-utility ratio of $98,000 per QALY falls in between breast screening with annual mammography for women over the age of 50 ($22,000/life-year) and heart transplantation ($160,000/life-year). Sensitivity analysis was performed to evaluate the stability of the model by varying the parameters of both the willingness to pay (from $25,000 to $300,000 per QALY gained) and the incidence of cancer (from 0–4% annually). Assuming a cancer incidence of 0.4% annually, surveillance every five years is the preferred strategy if the budgetary constraint were $100,000 or $300,000 per QALY gained. As the cancer incidence in BE patients increases, more frequent surveillance not only becomes more effective but becomes more cost-effective at each budgetary limit. The other parameter for which there is a great deal of uncertainty is the quality of life after esophagectomy. Sensitivity analysis indicated that without consideration of cost, at a baseline of 0.97, surveillance every five years is the preferred strategy. The threshold below which the morbidity of esophagectomy outweighs any gains in cancer prevention or cancer death prevention, was found to be 0.86.

An update of these results using an annual discount rate of 3% per year indicate that no surveillance costs approximately $5000 and provides 15.6 additional QALY. Surveillance every five years costs $17,000 and provides 15.85 additional QALY, yielding an incremental cost-utility ratio of $49,500 per

QALY gained. Sensitivity analysis on the incidence of cancer and quality of life after esophagectomy indicate that surveillance every five years is the preferred strategy with a budgetary constraint of $100,000.

These results suggest that surveillance of BE patients is effective. Surveillance every five years will reduce cancer deaths and have incremental cost-utility ratios comparable to those of common practices. The cost effectiveness of surveillance is based on the budget or willingness to pay of those who make health policies. Future efforts should target areas of greatest uncertainty, including the incidence and natural history of BE and the quality of life in BE patients. Sandler has proposed a randomized trial of surveillance every two *versus* every four years with an endpoint of high-grade dysplasia. Tissue and blood samples would be archived for DNA analysis, and for analyses of other potential risk-stratifying markers or factors. An economic analysis and a quality of life study of patients surveyed at these alternative intervals would be included. Eloubeidi found no differences in quality of life among BE patients and GERD patients without BE, using the SF36 general health status measure and a GERD-specific measure of quality of life [64]. Both groups scored well below average on the SF36; GERD symptoms were associated with bodily pain, impaired social functioning, and low emotional and physical functioning, suggesting a profound impact of GERD on daily living. A scenario-based utility assessment tool to study quality of life in BE patients is under development at Duke University.

Recommendations:

1. Define incidence of cancer and natural history
2. Quality of life: New tools

GLENN EISEN, Vanderbilt University

Promoting Data Quality in Population-based Screening and Surveillance

Over the past 30 years, the incidence of esophageal cancer has sharply increased. The NCI's Surveillance, Epidemiology and End Results (SEER) program data show 100% increase from 1974–1987 with a continued increase of 6–8% every year. Previously, esophageal adenocarcinoma represented < 8% of all esophageal malignancies; it was considered so rare that it was not separately categorized. The increased incidence was originally thought to be due to diagnostic misclassification, but no concurrent change in the squamous cell cancer incidence has been observed. BE is linked to this malignancy, with relative risk estimates ranging from 30–125 fold. Recently, the severity and duration of GERD has also been linked to esophageal adenocarcinoma risk [77]. However, the incidence of cancer development in BE appears to be significantly less than previously thought. Shaheen noted a possible publication bias in the reporting of cancer risk in BE, favoring small studies that show a positive link [44]. Nonetheless, even if the incidence is as low as 0.5% per year, 3,000–4,000 cases of esophageal cancer related to BE may be seen in the US every year. Prognosis is poor once adenocarcinoma is diagnosed, with five year survival < 8%. There is a suggestion of increased survival with earlier detection of high-grade dysplasia and cancer.

The estimated prevalence of BE ranges from 6–12% [9,29,32,33,41,89]; much of the variability stems from lack of consensus regarding the definition. Cameron compared the clinically-diagnosed prevalence (22.6 per 100,000) to the prevalence in a prospective autopsy series (376 per 100,000) and suggested that only one of 20 BE patients is being diagnosed [9]. This low detection rate may be due to the lack of specific symptoms. BE appears to make the esophagus less acid-sensitive; Lagergren noted that 40% of patients diagnosed with esophageal cancer had no antecedent reflux [77].

Although Norman Barrett (1950) discovered BE, some advocate removal of his name from the disease category because he incorrectly interpreted the condition as a congenitally shorter esophagus [59]. In 1953, Allison and Johnstone posited that BE was indeed the esophagus and not the stomach [60]. Moersch linked BE to GERD in 1959 [90]. Hayward, an Australian surgeon, proposed in 1961 that BE was a specialized junctional epithelium akin to the esophagus and the stomach [61]. Paull identified three types of epithelium that could constitute BE: junctional, fundic or specialized columnar lined epithelium (CLE) [91]. CLE is now commonly accepted as BE. Up to 15% of US pathologists nonetheless continue to misclassify junctional and fundic epithelium, which are not associated with cancer risk, as BE. A clear linkage between CLE, dysplasia, and cancer was established in the 1980s. It is difficult to discriminate SSBE from gastric cardia intestinal metaplasia. Identification of the GE junction can be made by differing criteria (anatomic, radiologic, physiologic, and endoscopic, which do not necessarily agree) and is complicated by movement of the esophagus and the asymmetry of the LES. General consensus holds that, on endoscopy, the GE junction is the proximal margin of the gastric folds, after insufflation of the esophagus [92,93].

Consensus is lacking on whether SIM at the GE junction bears the same cancer risk as BE. Immunoreactivity patterns for cytokeratins 7 and 20, and for the colonic goblet cell antibody DAS-1, are comparable in LSBE, SSBE, and SIM at the GE junction [94,95]. Hirota found different demographics, with LSBE and SSBE differentially predominanting in white males without *H. pylori* infection. Although dysplasia and cancer were considerably more common in LSBE, SSBE and SIM at the GE junction may have a larger impact on cancer burden because of increased prevalence [28].

BE surveillance is more akin to that for ulcerative colitis than colorectal cancers, the latter being significantly facilitated by visible polyps. The BE segment is usually grossly homogeneous. Endoscopic mapping can reliably locate areas of dysplasia, and this is essential for chemoprevention studies [96,97]. In a study of 30 esophagectomy specimens, Cameron found the following median surface areas: BE, 32 cm^2; low-grade dysplasia, 13 cm^2; high-grade dysplasia, 1.3 cm^2; adenocarcinoma, 1.1 cm^2 [98]. Up to 73% of resected specimens for high-grade dysplasia harbor occult cancer. Although these results suggest a low likelihood of finding high-grade dysplasia and cancer by random biopsy, an intensive, systematic biopsy protocol may be able to safely discriminate BE from cancer. Nonetheless, a significant interobserver variability in diagnosis of dysplasia persists. Concurrent erosive esophagitis may also obscure visual recognition of BE and pathologic interpretation of dysplasia [99]. Alternative tools for screening and surveillance include magnification endoscopy, chromoendoscopy, tissue spectroscopy (optical biopsies), balloon cytology, and mapping.

Screening recommendations for BE are based on single-center studies with limited follow-up; population-based studies are lacking. Screening criteria that are not well-defined include age, ethnicity, gender, BMI and GERD. The mean age for BE is 55 years; BE is dramatically increasing in white males, with a 3–7:1 male:female ratio. The threshold for risk factors such as chronic GERD and increased BMI is unknown [63,100]. Prevalence of BE on endoscopy is less than 5% in all comers, as compared with 12% of GERD patients and 35% of those with erosive esophagitis [29,101]. Unlike esophageal adenocarcinoma, BE is therefore not likely to be amenable to analysis through a claims or registry database. The CORI database includes 221,229 total EGDs for 162,226 total patients for the period April 1997 through September 2000. Of the 49,876 EGDs performed from 9/1/98 to 8/31/00, 9615 were indicated for GERD, 10,313 for dysphagia and 28,036 for neither GERD nor dysphagia. Suspected BE was found in 11, 5 and 3% of those for GERD, dysphagia, or neither, respectively; suspected cancer was found in 0.01, 2 and 0.2% of those for GERD, dysphagia, or neither, respectively. The CORI database is limited to GI practices and to patients referred for endoscopy. Although still a potentially powerful tool, limitations that could be improved upon include:

– No pathology
– No consensus/standards on screening, surveillance, and biopsy techniques
– Limited risk factor assessment
– Lack of standardized data fields.

Therefore, screening and surveillance efforts should incorporate central pathology review, standard instruments, standardized techniques, and longitudinal follow-up of subjects. Such studies should focus on establishing population-based estimates of the prevalence and natural history of BE. Investigation of the risk for adenocarcinoma development in BE is also a high priority. Screening studies should utilize modalities that are safe, inexpensive and systemic.

Recommendations:

1. Population-based estimates of BE prevalence, natural history, adenocarcinoma risk
2. Large scale, multicenter efforts at screening and surveillance
   – Defined cohort of interest
   – Central pathology review
   – Standard instruments
   – Standard techniques
   – Longitudinal follow-up of subjects
3. Targeted screening
   – Inexpensive
   – Safe
   – Systemic

MIMI CANTO, Johns Hopkins University
Novel Screening Techniques

BE is defined as histopathologically confirmed specialized columnar epithelium (SCE) of any length in the esophagus. Even if GERD patients are targeted for BE and cancer screening, the population is sizable; 4–9% and 20% of the US population have heartburn on a daily and weekly basis, respectively. Lagergren established a dose-response relationship for GERD in terms of the severity of reflux symptoms combined with duration [77], which should perhaps be considered in selecting patients for BE screening. Screening techniques include transnasal balloon cytology and endoscopy. At present, transnasal balloon cytology has limited potential for screening; the technique did not confirm SCE in 17% of 63 [102] and 100% of 10 [103] patients with biopsy-proven BE.

Methods to improve diagnosis of SCE include high-magnification endoscopy, chromoendoscopy, and immunostaining for cytokeratins and other markers. Chromoendoscopy entails topical application of chemical pigments or stains during endoscopy with the purpose of altering tissue appearance and improving localization, characterization, or diagnosis. Although not a novel technique, chromoendoscopy has recently received renewed interest because it is quick, simple, inexpensive, readily available, effective, and accurate. Woolf showed that Lugol's stain, which stains squamous mucosa but not BE, enhanced the diagnosis of BE with 91% accuracy, 89% sensitivity and 93% specificity compared with histology [104]. The stain is particularly useful for locating residual BE islands following PDT or ablation. Acetic acid can also be used in high magnification endoscopy to improve BE detection.

The vital stain methylene blue was evaluated in a pilot study of 26 patients (14 with biopsy-proven SCE; and 12 controls: 3, CLE with no SCE; 4, GERD and no CLE; 5, neither GERD nor CLE). A 95% accuracy, a mean cost of $9, a mean staining time of five minutes and a 43% diagnosis of SCE by directed biopsies in controls was found [105]. In a randomized comparison, detection of SCE in biopsies was significantly increased from 69% by 4-quadrant biopsy every two centimeters to 91% by methylene blue directed biopsy [106]. In a study of 51 patients with CLE, Kiesslich found a 98% sensitivity, a 61% specificity and positive and negative predictive values of 89% and 92%, respectively [107]. Low specificity was attributed to the presence of esophagitis.

Challenges in BE surveillance include limited data on natural history of dysplasia in BE, sampling error, and variation in biopsy technique. Grading of dysplasia is also subject to variability. The optimal surveillance technique or interval is not known. The time, equipment, staff, and expense required by biopsy protocols is significant. High variability was found in BE surveillance practices, particularly among the intervals and technique employed for low-grade or no dysplasia [83]. Greater consensus was found for management of high-grade dysplasia, with 73% of practitioners offering surgery. The national annual expense was estimated at $22 million; the practice variation alone contributed significantly to the cost.

An additional concern is that dysplasia and cancer are not likely to be apparent, and may be present as a tiny area within long segments of nondysplastic BE. Methylene blue enables visualization of focal

areas of high-grade dysplasia or cancer, and in fact heterogeneity of methylene blue staining is an excellent predictor for dysplasia. This has potential in selecting patients for aggressive biopsy, close follow-up and/or treatment. In patients who underwent random biopsy and methylene blue-directed biopsy 4–8 weeks apart, methylene blue-directed biopsy significantly increased the diagnostic yield of dysplasia from 8 to 19% [105]. Methylene blue staining also significantly reduced the number of biopsies required for diagnosis of dysplasia, particularly in patients with $ 3 cm of BE. In some cases, it found cancer that was missed by four-quadrant random biopsy every two cm. Methylene blue-directed biopsy was estimated to be less costly and also more cost effective than four-quadrant random biopsy every two cm. However, a benefit of methylene blue staining has not been universally found. Jobson [108] found no increase in diagnostic yield for SCE, and Breyer [109] demonstrated only a 73% sensitivity and 59% specificity for the technique. Diagnosis of dysplasia was increased by methylene blue-directed biopsy *versus* random biopsy (58% *versus* 46%), although the finding was not significant [110]. Finally, Gossner used methylene blue-directed biopsy for surveillance and found it produced a comparable rate of diagnosis of dysplasia or cancer, but required fewer biopsies than random biopsy [111]. Ongoing efforts to improve diagnosis include development of a double dye (methylene blue and crystal violet) technique to detect early flat cancer [112].

Future efforts should employ novel diagnostic modalities to study the natural history of GERD and BE, and to evaluate interventions. For example, methylene blue could be used to map the distribution, extent, and rate of development of CLE, SCE or dysplasia over time and in relation to therapies. A screening study could be conducted in the highest risk population (severe, long duration GERD), stratified for risk factors, with an endpoint of dysplasia, cancer or SCE prevalence. A BEST type of trial could define the optimal screening and surveillance technique(s). Finally, development of noninvasive markers of BE or esophageal cancer would obviate the use of endsocopy for screening and surveillance. Translational studies that examine, for example, the role of COX-2, prostanoids, and transcriptional silencing of tumor suppressor genes (*e.g.*, p16, APC) by promoter hypermethylation in BE should bank specimens for prospective use in marker development. Ideally, future screening programs could employ a panel of blood, saliva, stool or esophageal cell biomarkers.

Recommendations

1. Novel techniques to improve understanding of natural history of GERD, BE
2. Evaluate clinical significance of CLE at GE junction
3. Screening for BE/CA: Who? How?
4. Optimal screening/surveillance technique
5. Identify new risk biomarkers: enable noninvasive screening/surveillance

JACQUES VAN DAM, Stanford University
Novel Clinical Imaging Technologies

Methods to detect dysplasia include surveillance and random sampling, vital dyes and high magnification

endoscopy, optical coherence tomography (OCT), laser-induced fluorescence spectroscopy, and reflectance spectroscopy. The following paragraphs review the application of laser-induced fluorescence spectroscopy, light-scattering spectroscopy, and OCT in BE.

Laser-induced fluorescence spectroscopy was first used to detect dysplasia in the colon. In a comparative study of adenomatous polyps and adjacent endoscopically normal-appearing mucosa, fluorescence intensity could discriminate dysplastic from normal tissue [113,114]. An algorithm was developed to provide an assessment of low, medium, and high probability for dysplasia based on laser-induced fluorescence. The sensitivity and specificity could be modified by varying selected thresholds appropriate for a particular patient population (based in part on Baye's theorem). When the technique was applied to esophageal cancer detection, laser-induced flourescence was able to detect cancer and high-grade dysplasia of the esophagus with very good sensitivity. However, low-grade dysplasia detection was problematic.

In situ detection of dysplasia in BE can also be achieved with light-scattering spectroscopy, which can measure epithelial nuclear enlargement and crowding [115,116]. This measurement more closely approximates the criteria used by pathologists in assigning dysplasia grade, with dysplastic nuclei being larger, more crowded, and more darkly stained due to increased chromatin content. However, the spectroscopic method is more objective and has the potential to permit real-time assessment. A 90% sensitivity and specificity was found for the assessment of dysplasia (high- or low-grade, indeterminate, or none) by white light-scattering spectroscopy compared to histopathologic biopsies in 49 BE patients; the sensitivity for high- and low-grade dysplasia was 100% and 87%, respectively. Assessment of nuclear size and crowding by white light-scattering spectroscopy has since been achieved in a number of biological tissues including colon, oral mucosa, and bladder.

OCT provides high resolution images of tissues. Developed and first used successfully in ophthalmology, OCT has been applied to GI tissues in the last four years with recent publications of real-time assessment during endoscopy for BE [117–119]. OCT provides a 10-fold greater, with potential for a 100-fold greater, resolution than ultrasound. In contrast with ultrasound, OCT requires no liquid medium and the signal is not attenuated by air. The OCT probe resembles the optical fiber used in spectroscopy. Future applications for OCT include solid tumors, such as prostate, breast, and pancreas.

Future considerations for imaging of BE include using a combination of techniques, such as light scattering and fluorescent spectroscopy. Since each works through a different mechanism, each provides information lacking by the other, and the combination may be more sensitive than either modality alone. The application of spectroscopic OCT to endoscopy is experimental, but does represent a powerful combination of imaging techniques that may generate a "functional image" which includes data on nuclear size and crowding. Another novel technology with considerable potential for screening is the miniature CCD. The prevalence of BE, the denominator in the risk equation, is not known. Not all BE patients are symptomatic and undergo endoscopy; to establish the true prevalence,

the asymptomatic population should be screened. The CCD can be mounted on a guide wire; such a device would have a cost comparable to an otoscope or opthalmoscope, and could likewise be used by the primary care practitioner. BE patients, once identified in the primary care setting, could undergo more rigorous examination for dysplasia and cancer.

Recommendations:

1. Technology combinations:
   –Light scattering and fluorescence/reflectance spectroscopy; "trimodal spectroscopy"
2. Miniature CCDs: Primary care screening

BRIAN REID, Fred Hutchinson Cancer Research Center
Improving the Predictive Performance of Endoscopic Screening and Surveillance

The rationale for BE screening can be summarized in the following four statements:

1) The incidence of esophageal adenocarcinoma has rapidly increased [1].
2) Reflux symptoms are a risk factor for esophageal adenocarcinoma [77], providing a rationale for screening the GERD population.
3) Intestinal metaplasia or BE is the only known intermediate that can be used for early detection.
4) Esophageal adenocarcinoma has < 10% five-year survival [120].

The case against screening for BE is as follows:

1) GERD is common in the US population; 42% have symptomatic heartburn and 18% have weekly heartburn [8].
2) 88% of GERD patients do not have BE [29].
3) 40–50% of patients who develop esophageal adenocarcinoma have no history of GERD symptoms [77].

Based on these considerations, it is not clear whether screening should be GERD- or population-based. An additional concern is that current screening modalities (endoscopy with biopsies) are invasive and costly. Non-endoscopic screening modalities are more likely to attain widespread use in the primary care setting. Such approaches include blood testing for inherited susceptibility and somatic lesions, and colorimetric screening for BE. A high correlation was found for detection of BE by the colorimetric assessment device and by endoscopy, with comparable identification of BE islands and tongues [121].

Identification of a "BE gene" would facilitate population-based screening as a means of selection for endoscopic screening and surveillance. Two recent studies demonstrating little evidence of familial aggregation dampen enthusiasm for finding such a gene [45,122]. Moreover, the rapid rise in incidence suggests that the disease is driven by environmental rather than genetic factors. Somatic lesions involved in BE may include the APC gene. Loss of APC by hypermethylation of the promoter region occurred in abnormal esophageal tissue in 92% of 52 patients with esophageal adenocarcinoma and in about 40%

of 43 patients with BE, but not in matching normal esophageal tissues [72]. Hypermethylated APC was found in the plasma of 25% of esophageal adenocarcinoma patients, and high plasma levels were significantly associated with reduced patient survival. Unfortunately, this marker was not found in the plasma of BE patients.

A cohort study from van der Burgh makes a strong case against endoscopic surveillance in BE [123]. This study followed 155 BE patients for a mean of 9.3 years without surveillance, an approach unlikely to be tolerated in the US. The mean age at intake was 62 years. Of the 79 deaths, only two (2.5%) were due to esophageal cancer. An important additional consideration for endoscopic surveillance is cost-effectiveness. A five-year BE surveillance interval is cost-effective compared to cervical cancer screening; shorter intervals may be cost-prohibitive, as may be the five-year interval if indeed cancer incidence is lower than the assumed 0.4% [124]. In practice, however, surveillance intervals are much shorter than five years [82]. About 90% of patients without dysplasia undergo surveillance every year or every other year, and 70% of patients with low-grade dysplasia are surveyed every six months or more frequently. Ofman found a significant economic impact of transient diagnoses of dysplasia in BE, which accounted for up to 61% of all endoscopies and yielded an incremental 10-year cost of more than $500,000 [125].

Biomarkers may offer an attractive alternative or adjunct to surveillance of dysplasia in BE. In order of progression, candidate biomarkers for BE include p16, clonal expansion, 17p (p53) LOH, increased tetraploidy (4N), and aneuploidy. As cancer progresses, both field size and ease of biomarker detection decrease. Many studies support the notion that p16 and p53 lesions have the biggest field size, and are the easiest to detect; in contrast, high-grade dysplasia is small, patchy and difficult to detect, and cancer is yet harder to detect [76,98,126–131]. A recent study showed that if a small cancer is present at baseline endoscopy, six biopsies every one centimeter are required for detection. However, detection of such a cancer on follow-up requires an average of 24 biopsies every centimeter [127].

The predictive values of histology and flow cytometry were comparatively assessed in 300 patients followed for up to 15 years; the endpoint was cancer development within five years of baseline endoscopy [76]. Either histologic diagnosis of high-grade dysplasia, or increased 4N or aneuploidy on flow cytometry, was found at baseline endoscopy in all patients who developed cancer within the subsequent five years. When considered alone, histology based on 3½ biopsies detected 80%, suggesting a minimal yield of the fourth standard biopsy. Surprisingly, flow cytometry (requiring only ½ biopsy per level) alone detected 76% of the patients who developed cancer. This study implies that histologic diagnosis of dysplasia is unlikely to be both safe and cost-effective for long surveillance intervals.

A prospective study found that 93% of 26 patients who progressed to cancer during follow-up had 17p (p53) LOH and/or aneuploidy at baseline. The abnormality was detected using a single biopsy every two cm. Analyses of LOH at chromosomes 9 and 17 in more than 1800 biopsies from 300 BE patients

with nearly 28,000 genotypes indicated that this p53 mutation may "hitchhike" on clonal expansion driven by loss of p16. Nearly 60% of clonal expansions throughout the BE segment involved 9p LOH at loci linked to p16. Moreover, 65% of all p53 clonal expansions could be attributed to p16-deficient clonal expansions; p16 loss in the remaining 35% may arise through mutation or promoter hypermethylation, mechanisms not examined in this study. A cluster of 52 genes (which could serve as biomarkers for BE) was identified in the p53 -/- 4N molecular phenotype using array analyses. Forty-three of these are known genes, of which 34 are G_2/M genes. It is hypothesized that p53 checkpoint loss leads to formation of a tetraploid cell that has mitotic instability. This leads to further genetic instability and the development of aneuploidy.

One strategy to rapidly and broadly implement advances in genetics and technology development within the BE research community would be to establish a research network. This network could also facilitate screening and surveillance studies. As a population-based problem, screening will require alternatives to the endoscope. Ideally, a low-cost, non-invasive modality would be employed. Endocrine and paracrine factors in BE could potentially be screened in blood. Stool or gastric aspirates could also be screened for molecular lesions associated with BE. Minimally invasive but low cost approaches include ultra-thin endoscopes and colorimetric screening devices. Surveillance is a clinical management rather than a population-based problem that would benefit from smart endoscopes, which could potentially detect underlying genetic changes. Histology is unlikely to be both safe and cost-effective; biomarker alternatives should be evaluated in five-year follow-up studies to assess correlation with outcome. An emerging question regarding new approaches is whether they will be used as an adjunct to, or will replace, standard pathologic diagnosis.

Recommendations

1. BE research network
2. Screening:
   - Low cost, noninvasive screening (endocrine or paracrine factors in blood, stool, saliva) or minimally invasive screening (ultrathin endoscopes, gastric aspirate, colorimetric device)
3. Surveillance:
   - Smart endoscopes
   - Histology alone unlikely to be safe and cost-effective
   - New biomarkers
   - Adjunct to standard pathology *versus* new diagnostics

GROUP DISCUSSION AND RECOMMENDATIONS

Discussion Leaders: Sandy Dawsey and Ernie Hawk

The following critical research questions in BE were identified:

- Why is the incidence of esophageal adenocarcinoma increasing?

- How can mortality be reduced?
- What is the true prevalence of BE (estimated at 6% in GERD patients)?
- Who should be screened for BE and how?
- When does BE develop, and what is the natural history of the disease?
- Once the BE cohort is identified, what is appropriate management?
- What is the best approach for detection of dysplasia?
- What is true cancer risk in BE (estimated at 0.4–1.0 % annually)?

Strategies to address these issues should include high-risk/high-yield and lower-risk/lower-yield approaches. Three recommendations were discussed:

1. Surveillance trial would:
   - Establish appropriate management (surveillance intervals) of BE patients, including those identified by population-based screening efforts
   - Possibly be modeled on the National Polyp Study
   - Require multicenter scale and infrastructure
   - Employ standardized biopsies, tissue and blood banking, biomarker development
   - Have high-grade dysplasia as endpoint (estimated to require 3550–5000 patients, 14 sites, five years)
   - Establish incidence of high-grade-dysplasia and/or cancer
   - Establish natural history, risk factors
   - Take advantage of the unique opportunity provided by BE to study cancer progression
   - Provide wealth of data on BE regardless of outcome
   - Have little overall public health impact, but esophageal cancer incidence is increasing
   - Raise concern that technology could become outdated during course of study unless it is short
   - Be more feasible at present than screening study

2. Screening study would:
   - Have as rationale that cancer incidence is increasing despite surveillance
   - Establish BE cohort
   - Establish risk factors, etiology
   - Establish denominator in risk equation (prevalence)
   - Require study population
     – With, without GERD (standardized questionnaires needed)
     – May need to involve primary care physicians as source for referrals
     – Colonoscopy screening population would provide ready access to patients, but may introduce selection bias
     – May require up to 50,000 subjects
   - Need technologies for screening in the primary care setting (*e.g.*, thin endoscopes, gene-based imaging, blood-borne biomarkers)
   - Raise concern that technology could become outdated during course of study

- Raise question of whether it is appropriate to invest in identification of cohort in the absence of established management practices
- Feed surveillance efforts

3. Network/consortium would be:
   - Cooperative group focused on premalignant conditions of the GI or upper GI tract
   - Means of rapid access to new technologies (development adequately supported by alternative mechanisms, *e.g.*, SBIR, R01, industry)
   - Necessary for surveillance, screening, and intervention studies:
     – clinical infrastructure
     – methodology, biomarker development
     – tissue/blood banking
     – only mechanism to provide adequate study population
     – systematic questionnaires, data collection, informatics

Recommendations:

1. Establish a multicenter, multidisciplinary research network to facilitate cohort, screening, surveillance and intervention studies in BE.
2. Conduct a surveillance trial to establish the natural history and clinical management of BE.
3. Conduct a screening study in a broad-based population of asymptomatic and symptomatic patients to establish the incidence, prevalence, risk factors and etiology of GERD and BE.

CHARLES LIGHTDALE, Columbia University
Endoscopic Treatment of Barrett's Metaplasia/Dysplasia (Treatment Guidelines)

BE probably arises as a result of chronic injury to the esophagus from stomach acid refluxate. Once established, BE progresses to adenocarcinoma through progressive molecular abnormalities, reflected in light microscopic changes that are characterized as low-grade and high-grade dysplasia. These changes occur over months and years with no associated symptoms. Although BE is an occult disease, the protracted time to cancer development creates an opportunity for intervention. Intervention strategies include endoscopic surveillance, which is instituted once BE is identified. Medical acid suppression or anti-reflux surgery are commonly employed, at least for symptom control. Other strategies include endoscopic ablation therapy, the focus of the discussion below, as well as chemoprevention and esophagectomy.

The strategy of endoscopic ablation of BE for esophageal cancer prevention is an extension of the considerable and successful experience of polyp removal in colon cancer prevention. Ablation combined with acid reflux suppression was shown to cause partial, or in some cases complete, healing with squamous mucosa [132,133]. Contact thermal ablation methods include multipolar electrocoagulation (MPEC) and the YAG laser. Non-contact thermal ablation can be achieved with lasers (Nd:YAG, argon, KTP), the argon plasma coagulator, and PDT. Endoscopic mucosal resection (EMR) entails submucosal fluid injection to create a polypoid-like mucosal area that can be resected with a cautery snare, comparable to colon polyp removal. EMR is employed primarily for focal lesions and, unlike other ablative methods, provides a specimen for histopathologic evaluation. Experimental ablation methods include cryoablation and high frequency ultrasound.

Immediate risks of endoscopic ablation therapy include pain, dysphagia, nausea, hemorrhage, perforations, and stricture. Of greater concern is the potential for cancer development from residual metaplastic or dysplastic columnar tissue beneath new squamous mucosa. Although SSBE was eradicated in 51/52 patients treated with MPEC, columnar glands were evident underneath the new squamous mucosa in 11 patients on six-month follow-up with four-quadrant biopsies. Patients underwent an average of 3.6 sessions and were treated with 40 mg omeprazole bid [134]. Considerable controversy exists regarding the required extent of acid reduction following ablation therapy. Twenty-four hour pH monitoring indicates that BE patients require higher doses of proton pump inhibitors for acid reflux elimination than do GERD patients. Reflux contents (*e.g.*, bile salts), inflammatory processes, and other factors may also affect regeneration of squamous tissue following ablation therapy.

Three studies of argon plasma coagulation found fairly high percentages (22, 30 and 47% respectively) of residual intestinal metaplasia under new squamous epithelium on follow-up of 9, 30 and 31 treated

patients [135–137]. Byrne also reported two perforations, one resulting in death. A multicenter study in Germany found only 1% residual intestinal metaplasia using much higher voltages and gas flows, and high-dose omeprazole in 70 patients [138]. Likewise, Pereira-Lima [139] reported only a 3% rate of residual intestinal metaplasia in 33 patients; however, three strictures occurred in each of the two latter studies. Although successful, more aggressive ablation causes higher complication rates.

The cancer risk is estimated at 0.5% per year for BE metaplasia; however, low-grade and high-grade dysplasia confer higher cancer risks of 18% over 4.3 years and 34% over 4.5 years, respectively. Standard of care for BE patients with high-grade dysplasia is now esophagectomy, which has an operative mortality of 4–7%, early morbidity of 15–32%, and significant long-term morbidity (75%). Importantly, there is risk of recurrent intestinal metaplasia/dysplasia and even cancer in the esophageal remnant [5,140]. This problem is compounded by the increased incidence of dysplasia and cancer with age [141], with significant comorbidity elevating surgical risk in older patients. These findings support endoscopic ablation therapy for BE patients with high-grade dysplasia. Appropriate and perhaps feasible goals for this population might be to ablate BE with high-grade dysplasia and any occult microinvasive carcinoma, to encourage squamous mucosa regrowth by acid reflux suppression, and to thereby decrease or eliminate esophageal cancer mortality.

Endoscopic ultrasonography (EUS), particularly with higher frequency (20 or 30 MHz) probes, may improve staging of early esophageal cancer to select focal lesions for EMR. Of concern is that even submucosal (T1) esophageal cancer may not be appropriate for EMR due to the $ 25% risk of lymph node metastases. Ell removed 35 nodular or flat lesions that were T0 or T1 on EUS; no submucosal invasion was found on pathology. The only complication was mild bleeding in one patient, and 97% of patients had no evidence of disease on 12-month follow-up [142]. EMR was also performed as an outpatient procedure on 23 Mayo clinic patients with T0 or T1 lesions on EUS; 46% of the lesions were nodular, and 54% were suspected high-grade dysplasia or T1. Adenocarcinoma was found in 52%, and high-grade dysplasia in 16%. No complications were reported [143].

Multiple EMR applications have been used to remove BE from half the circumference of the esophageal lumen; strictures are inevitable with more extensive treatment. A combination of ablation techniques (EMR, PDT, argon plasma coagulation, and MPEC) was employed in 10 patients (three with T1 cancer, seven with high-grade dysplasia) with a mean age of 76. On 14-month follow-up, seven had no evidence of BE on systematic biopsies of the treated areas. One had residual low-grade dysplasia, and two had residual BE. Complications included one stricture. PDT has also been combined with EMR in 17 Mayo Clinic patients with superficial cancer in BE. All were in remission at a mean follow-up of 12 months. Three strictures occurred.

Although feasible, endoscopic ablation therapy of BE remains experimental and offers no proven benefit. The major limitation is the risk of residual columnar epithelium beneath the new squamous epithelium. However, ablation may be appropriate in BE patients with high-grade dysplasia or mucosal cancer who are at increased surgical risk. EMR appears safe and effective for focal lesions. Research

areas include the development of improved endoscopic ablation methods, and better use of existing methods. Post-injury regeneration mechanisms should also be explored and potentially manipulated to favor squamous *versus* columnar regeneration. The development of non-ablative endoscopic methods for local injection of substances or gene therapy should also be pursued. Combinations of endoscopic therapies, and of endoscopic modalities with other therapies such as pharmacologic and molecular treatments, are also promising. In this regard, endoscopic ablation could be used for debulking, and any residual microscopic disease could be treated with pharmacologic or molecular methods.

Recommendations:

1. Improved ablation methods
2. Post-injury regeneration mechanisms
3. Non-ablative endoscopic methods
   – Genes
   – Drugs
4. Combinations of endoscopic and medical prescriptions

KEN WANG, Mayo Clinic
Photodynamic Therapy of Barrett's Metaplasia/Dysplasia and Cancer

PDT has three basic components: light, drug (photosensitizer), and oxygen. The porphyrin derivatives Photofrin 1 and 2 are approved and used in the US. These photosensitizers are a mix of polymers–oligomers, trimers and dimers; FDA mandates use immediately after mixing because the composition is unstable over time. Aminolevulinic acid (ALA) is a pure compound that is not available in the US for systemic use but is currently in Phase III testing for topical applications. Other photosensitizers include Lutex (lutetium texaphyrin) and the British drug Foscan. Each photosensitizer has distinct properties and cell-type specificity. For example ALA is concentrated in the cytoplasm where it is converted to protoporphyrin IX. Selectivity of ALA for mucosa *versus* muscle makes it attractive for superficial therapy of BE. Hundreds of new agents of varying specificity in the GI tract are in preclinical development. Once absorbed in the esophageal mucosa, the photosensitizer is activated to a stable, high-energy triplet state by red light (630 nm light is used in the US). Interaction with molecular oxygen yields singlet oxygen, which in turn produces cell damage. Effects are dependent on the timing of light activation; a short or long interval post photosensitizer administration will respectively cause cytoplasmic or nuclear damage. However, the clinical consequences of varying this interval have rarely been explored.

The clinical technique is simple: two days post Photofrin 2 injection, an endoscope fitted with a small (2.5–5 cm) fiber is used to photoradiate the esophagus. As with endoscopic ablation therapy, PDT is technically complicated by movement of the esophagus caused by breathing and swallowing during the procedure; this movement varies the distance between tissue and fiber and profoundly affects light dynamics. This issue stimulated development of the balloon diffuser by Overholt. Care must be taken to

avoid exerting excess pressure on the esophageal wall with the diffuser, as this will cause focal ischemia and preclude a photodynamic effect. After PDT, the mucosa sloughs in a relatively uniform manner.

The dysplasia response rate following PDT of BE patients with high-grade dysplasia ranges from 88–100% in published series [144–147]. However, the rate of total elimination of BE is only about 40%. Most report no effect of ALA on BE length, although a 30% decrease has been found. The response rate for T0 or T1 cancers is about 75% with a one year follow-up [144,146,148]. An ongoing multicenter trial has thus far randomized 208 patients with high-grade dysplasia to PDT or no therapy at a 2:1 ratio. Interim (six-month) results indicate a 62% response rate of high-grade dysplasia. This low response rate may be attributed to the early time of evaluation; however the study employed a low light dosage to avoid stricture. A significant difference was found in the primary endpoint of cancer development at six months, but this likely represents elimination of prevalent cancers.

The most common adverse event post Photofrin 2 administration is cutaneous photosensitivity that can persist for 30–90 days; it is not dependent on location (Florida *versus* Minnesota) or season. About two-thirds of patients experience photosensitivity, although most reactions are inconsequential, and serious events are extremely rare. Newer agents (Lutex, Foscan) cause a shorter, 1–2 week duration of photosensitivity, but the events tend to be more severe. The other major adverse event with PDT is stricture formation, which occurs in about 25–30% of patients. This high stricture rate, comparable to that seen after esophagectomy, bespeaks the severity of esophageal injury induced by PDT.

Of particular concern is whether PDT modulates cancer risk; residual islands of BE, and submucosal BE glands underlying normal squamous tissue, are commonly found after PDT. Overholt reported one cancer, two instances of high-grade dysplasia, and two instances of non-dysplastic BE underlying squamous tissue [144]. In this series, 83% of patients also received adjuvant YAG laser therapy; it is common to treat residual areas of BE after PDT by thermal endoscopic ablation modalities, for which fairly high incidences of submucosal BE is reported. Persistent BE islands may reflect non-uniform distribution of light or drug, or they may represent the focal presence of a more resistant phenotype. Although no single marker predicted the reappearance of high-grade dysplasia following PDT, abnormalities for aneuploidy, p16 and p53 persisted despite transient improvement in dysplasia grade.

PDT for BE could be optimized by several complementary strategies. Selection of appropriate patients is a priority; preliminary evidence suggests that p53 mutation may predict poor response. The dose and regimen of current photosensitizers have not been fully explored and many new agents are being developed. Because photosensitizers are fluorescent, drug levels (which are predictive of response) can be monitored real-time during endoscopy by laser-induced fluorescence. Light delivery systems are also in their infancy. Monitoring of results during and after treatment could also be improved. Post-PDT surveillance should employ "deep" biopsies that can detect submucosal BE. As an alternative or adjunct technique, Raman spectroscopy can be used to distinguish residual BE islands from gastric tissue. Biomarker development is critical to this effort. Adjuvant therapies could potentially be used to influence tissue regeneration following PDT. Possibilities under exploration include COX-2 inhibitors

and ursodeoxycholic acid; in BE animal models, cancer formation was significantly reduced by the COX-2 inhibitor NS-398 or sulindac.

Recommendations:

Strategies for PDT Optimization:

–Patient selection
–Photosensitizers
–Light delivery systems
–Dosimetry
–Monitoring of results ("deep" evaluations and biomarkers)
–Adjuvant therapies (combinations that influence regeneration)

BRIAN REID, Fred Hutchinson Cancer Research Center
Dietary and Molecular Interventions in Barrett's Metaplasia/Dysplasia

As discussed in the following paragraphs, potential interventions for BE include PPIs, dietary modification, selenium, NSAIDs, Onyx 015 (p53) and telomere length. Surrogate endpoints are required for efficacy testing of these interventions in randomized clinical trials. Ideally, such biomarkers would be validated as predictors of cancer incidence in prospective studies. In order of disease progression, candidate biomarkers for BE include p16, clonal expansion, 17p (p53) LOH, increased tetraploidy (4N), and aneuploidy. Those downstream of p53 have been validated as predictors of cancer progression, but earlier markers are needed. A fundamental issue is whether the intervention affects the biomarker as well as disease progression; for example, persistence of p53 lesions may predict a long-term cancer outcome, even if dysplasia transiently improves.

Ouata-Lascar examined the effect of acid suppression in BE patients during treatment for reflux symptoms with the PPI lansoprazole [149]. PCNA labeling (a measure of proliferation) was markedly diminished in patients with normalized acid exposure, while it remained elevated in those with asymptomatic but persistent reflux (as assessed by 24 pH monitoring). Sharma found BE beneath squamous islands in patients treated with PPIs [150]. These islands can progress to cancer, which limits the application of PPIs as chemopreventives

The rationale for dietary intervention is founded in a number of studies demonstrating that overweight, high-fat diet, and low fruit and vegetable intake are risk factors for esophageal adenocarcinoma. An ongoing trial at the Fred Hutchinson Cancer Center randomized 92 patients to an intervention of a medically prudent diet (low fat, high fruit and vegetables, elimination of foods causing reflux) with medical counseling, or medical counseling alone. The outcome (effects on cell cycle, tetraploidy and aneuploidy) is not yet known, but some of the goals have been met. By contrast with their control counterparts, both men and women in the intervention group experienced weight loss, decreased fat intake and increased fruit and vegetable consumption. Although most prior studies have focused on

effecting weight and dietary changes in women, this study demonstrates that such goals can also be achieved in men.

In an observational study, the lowest quartile of serum selenium showed a higher rate of elevated 4N than the upper three quartiles. This finding is also true of aneuploidy and p53 status. Those who never used NSAIDs also had a significantly higher rate of progression to aneuploidy than current NSAID users. Such studies will provide necessary data for the calculation of sample size and trial duration for further evaluation of these validated intermediate markers.

A Phase I dose-escalation trial of the p53 mutant adenovirus Onyx-015 was conducted in six BE patients. The one-time, three-hour delivery required that subjects be rotated every 20 minutes. Three patients developed cancer during follow-up. One had stable high-grade dysplasia for one year, and one regressed to indefinite for dysplasia for eight months. One patient regressed to GERD without BE for 11 months. On flow cytometry, two of six lacked aneuploidy or 4N abnormalities at baseline and follow-up. No evidence of toxicity was found.

Short telomeres might also be a target for intervention. In most BE patients, telomeres are relatively short until cancer develops, at which point telomerase is reactivated. Reintroduction of hTRT, the catalytic subunit of telomerase, into p53 null and wild type cells that have relatively short telomeres causes telomere lengthening. A single cluster of 52 genes overexpressed in p53 -/- 4N cells is also suppressed by reintroduction of hTRT. Forty-three of the genes are known; 34 are G_2/M genes.

Prevention strategies must take into account the low incidence of cancer in BE, which makes a cancer endpoint impractical. Observational studies are necessary to validate candidate surrogate endpoints. A major challenge is to develop alternatives to the three most widely reported, but not standardized, measurements in BE research: BE length, endoscopic appearance of the mucosa, and dysplasia. Three candidate molecular targets are proposed: p16, which is abnormal in 90% of BE; p53, which is abnormal in 90–100% of BE and cancers; and short telomeres. These lesions are among the most common in human neoplasia. Preventive interventions that would target these lesions must be safe. Delivery is also a critical issue; oral administration is ideal. Additionally, data necessary for agent development from preclinical through Phase III clinical testing must be accessible to investigators. Standard statistical analyses should also be employed. To achieve these goals, tools from clinical, public health and laboratory sciences can be applied to the development of preventives for BE and esophageal cancer.

Recommendations:

1. Clinical Sciences:
   - –Central path with molecular characterization
   - –Endpoint definition
   - –Delivery systems
   - –Support personnel

–Biological specimen repositories
2. Public Health Sciences
–Common data elements
–Standard questionnaire
3. Lab Sciences
–Genomics
–Biotechnology
–Biomarkers
–Bioinformatics
–Bioengineering

STUART SPECHLER, University of Texas at Southwestern
Pharmacologic Treatment and Cancer Prevention in Barrett's Metaplasia/Dysplasia

The overall incidence of esophageal cancer in the US has not risen significantly; it is the incidence of esophageal adenocarcinoma that has dramatically increased. The patient population has also changed, and is no longer predominantly comprised of alcoholics and heavy cigarette smokers. GERD is now considered a primary risk factor. The development of esophageal adenocarcinoma is believed to start with gastroesophageal reflux. Reflux damages the squamous epithelium, and ongoing reflux may be necessary for progression of squamous injury to intestinal metaplasia. Reflux may also drive development of dysplasia, and may thereafter cause genetic changes in the dysplastic epithelium that eventually lead to carcinoma.

Three goals of treating GERD in BE patients include elimination of GERD symptoms, prevention of GERD complications, and cancer prevention. Many studies clearly show that treatment can eliminate symptoms, and complications such as esophageal stricture and erosive esophageal ulcers can also be prevented. Nevertheless, most BE patients will continue to have pathological acid reflux while on dosages of PPIs that totally eliminate GERD symptoms [151]. Pulsed acid exposure *in vitro* stimulates cellular proliferation in BE explants [67]. Normalization of acid reflux with PPI therapy in BE patients was accompanied by a marked decrease in the proliferation marker PCNA and increase in the differentiation marker villin; however, these changes did not occur in the absence of reflux normalization [149]. Most BE patients treated with PPIs exhibit partial regression in the form of squamous islands. Intestinal metaplasia is found underneath these islands in about 40% of patients, and more than half of squamous islands show molecular abnormalities (p53, Ki-67). It is not clear that partial regression reflects a decreased cancer risk. Despite that ranitidine administration with twice-daily omeprazole can control nocturnal gastric acid breakthrough [152], evidence that this strategy would decrease cancer risk is lacking. Antireflux surgery is another treatment strategy for GERD; however, this surgery does not completely stop reflux and may not decrease dysplasia or cancer risk.

Several lines of evidence support the potential for COX-2 inhibitors in the prevention of esophageal

adenocarcinoma. COX-2 inhibition decreases growth of cancer cells and it decreases tumor formation in an APC knockout mouse. COX-2 is overexpressed in colorectal, gastric, pancreatic, and esophageal cancers. BE metaplasia, dysplasia and cancers all had significantly higher COX-2 levels than did squamous epithelia [153]. Acid or bile exposure increased COX-2 expression in BE explants; curiously, however, acid mixed with bile did not elevate COX-2 levels. The COX-2 inhibitor NS-398 decreased cell growth and increases apoptosis in esophageal adenocarcinoma cell lines that express COX-2, but was without effect on a control cell line that does not express COX-2 [154].

From 1986–1988, the VA cooperative study on reflux disease randomized 247 patients with complicated GERD to medical *versus* surgical therapies [155]. Surgery (open Nissen fundoplication) was superior to medicine (ranitidine, antacids, metoclopramide, and sucralfate) for controlling the symptoms and signs of reflux disease. A recent follow-up of 239 of these patients found 160 survivors of a mean age of 67 years. Survival in the surgical patients was decreased significantly compared to the medical group; 40% and 28% of the surgical and medical patients, respectively, were confirmed dead. Deaths from heart diseases (all types) were more common in the surgical groups. A total of five patients developed esophageal cancer, one in the surgical and four in the medical group; both esophageal cancer deaths occurred in the medical group. Four adenocarcinomas developed in the 108 patients who had BE with specialized intestinal metaplasia at baseline during more than 1000 patient-years of follow-up. The esophageal adenocarcinoma incidence rate was thus one cancer per 259 patients years, or a 0.4% incidence of cancer per year.

The risk of cancer in BE in absolute terms is low (estimated at 0.4–1.9%). The risk of GERD alone is yet lower, perhaps 0.07% per year; only one esophageal adenocarcinoma developed in 139 patients with severe GERD and no BE in the VA cooperative study follow-up. Certainly GERD and BE predispose to adenocarcinoma of the esophagus; although increasing in incidence, it nevertheless remains a relatively uncommon malignancy and death from esophageal adenocarcinoma is also infrequent. Neither medical nor surgical GERD therapy has been shown to prevent that cancer. An interesting calculation is the number needed to treat, which is the inverse of the actual risk reduction, for a given intervention to prevent one cancer per year. Assuming an annual risk for esophageal cancer of 0.5% and a 50% decrease in cancer risk with treatment, the absolute risk reduction would be 0.25%; thus, 400 patients would need to be treated to prevent one cancer per year. Such a strategy would only be acceptable if the treatment were safe, convenient and inexpensive.

A study on BE therapy that will have clear clinical implications must use a meaningful endpoint. Biomarkers such as proliferation and differentiation have not been correlated to clinical outcomes, and dysplasia may also not be an ideal endpoint because it is subject to significant variability. A cancer development or mortality endpoint, although meaningful, would require following thousands of patients for 5–10 years. Fifteen years ago, a clinical study on the impact of BE surveillance on mortality was considered impractical because the effort would require 10-year follow-up of a huge number of patients. With hindsight it is apparent that, had such a trial been initiated then, answers to some of the fundamental questions in BE would now be available.

Recommendations:

1. Endpoint definition is critical
   –Intermediate markers (proliferation, differentiation, *etc.*)
   –Dysplasia
   –Cancer development
2. Any trial will require:
   –Large patient numbers
   –Long duration of follow-up

ARLENE FORASTIERE, Johns Hopkins University
Therapy of Barrett's-related Adenocarcinoma

Esophageal adenocarcinoma is a low-incidence cancer representing about 1% (12,300 cases) of new cancers in the US. This is an underestimation because disease that straddles the GE junction is categorized as gastric cancer; this misclassification has impeded research and understanding of esophageal adenocarcinoma. The biology and the natural history of adenocarcinoma of the esophagus, GE junction and cardia are distinct from that of gastric cancer. This distinct disease entity is not identified by the current AJCC staging system. For example, 80% of adenocarcinoma recurrences are distant whereas 80% are locoregional in gastric cancer. A dramatic change in esophageal adenocarcinoma incidence has occurred in recent decades; in the 1960s, squamous cell carcinoma accounted for 90% of esophageal cancers, whereas 50–80% of the incidence is now adenocarcinoma. Squamous cell carcinoma affects black males six times more often than white males and is localized to the mid-esophagus. By contrast, adenocarcinoma is four times more common in white males and is distally located. Survival is not different for adenocarcinoma *versus* squamous cell carcinoma; five-year survival is about 18% (median 15 months) with surgery. Survival is greatly influenced by stage of disease, with a profound decrease from stage I to II and higher disease. This is likely due to the high probability of lymphatic involvement with later stage disease. The peak age of adenocarcinoma incidence is 65–75 years.

Treatment strategies have included surgical and nonsurgical approaches. Induction strategies of chemotherapy or chemoradiation followed by surgery developed in parallel starting at the end of the 1970s from the experience in head/neck and anal cancer treatment, respectively. With two or three cycles of preoperative chemotherapy, about half the patients will have a partial response to treatment and an occasional patient will have no tumor found in the surgical specimen. Induction chemotherapy was evaluated in a landmark study of 440 patients (two-thirds of whom had adenocarcinoma) by the GI Intergroup. At the same time, a very similar study was conducted in 802 patients by the Medical Research Council (MRC) in Britain. The MRC study was powered to detect a 10% difference and did in fact do that; survival rates at two years were 35% with surgery alone, compared to 45% with cisplatin plus 5-fluorouracil and surgery. Median survival was 13.4 months with surgery alone and 17.4 months with induction treatment. Mortality rates were about 10% with either treatment. The Intergroup

trial in the US found no survival difference by the addition of chemotherapy [156]. Median survival at two years was 37% with surgery alone, consistent with the MRC study control group, and 35% with chemotherapy plus surgery. Treatment mortality was about 6%, and the curative resection rate was about 60%, in either group.

Herskovic showed a significant increase in five-year survival with chemoradiotherapy compared to radiation [157]. Patients (nearly 90% of whom had squamous cell carcinoma) were randomized to either 64 Gy radiation or 50 Gy radiation with four cycles of cisplatin and 5-fluorouracil, two with and two after radiation. About 50% of patients received the two cycles after radiation. At the first interim analysis, randomization to radiation was terminated. At five years, the radiation alone group had no survivors, whereas the chemoradiotherapy group had a 26% survival [158]. However, at one year almost 50% of patients in the superior arm had persistent or recurrent local disease. The next study design used this superior arm as a control, and simply increased the dose of radiation hoping to improve local control. A minority of patients had adenocarcinoma. The study was closed after the first interim analysis because the high dose arm had more toxicity, including death, and lower two-year survival.

Three randomized trials examined the efficacy of combining all three modalities (surgery, chemotherapy and radiation). In a randomized trial of 113 adenocarcinoma patients, Walsh found a 32% 3-year survival with 40 Gy radiation and chemotherapy (cisplatin plus 5-fluorouracil) plus surgery, compared with 6% for surgery alone [159]. A University of Michigan study that included 75 adenocarcinoma and 25 squamous cell carcinoma patients suggested a long-term survival benefit of combined treatment on the order of 10 or 15%, but the study was designed to detect only much larger differences. Survival curves separated at two years, with pathologic complete responders showing a significant survival advantage thereafter. The pathologic complete response rate was comparable to that seen in Walsh's study of adenocarcinoma patients and a European study of squamous cell carcinoma patients [160], with values ranging from 25–30%. The median survival for the combined treatment arm ranged from 16–18.5 months.

Taken together, these studies suggest that combining preoperative modalities may improve local control; however, evidence of improved survival is limited. Preoperative chemotherapy or concurrent chemoradiotherapy thus remain investigational. For non-surgical treatment, chemoradiotherapy is standard of care, but local failure (recurrence plus persistence) is high. Unfortunately, increasing the intensity of chemotherapy or radiation appears to add toxicity without improving survival. Molecularly-targeted therapies may improve tolerance and efficacy. A number of genetic and cell cycle abnormalities have been identified in adenocarcinoma of the esophagus. For example, aneuploidy, p53 loss or mutation, and G1 and S phase cell cycle abnormalities have a prevalence of about 90%. Certain oncogenes (erbB2/p185 and cyclin D1) and tumor suppressor genes (Rb, p16, p53) are also commonly mutated in esophageal adenocarcinoma. Molecular profiling of esophageal adenocarcinoma could permit therapy to be individualized. The fact that esophageal adenocarcinoma is uncommon but has increasing incidence poses a major challenge for translational research. However, the tissue is readily accessible and amenable to repeated measurement. A new, multicenter administrative model

that would link scientific and clinical expertise could greatly benefit research in this area.

Recommendations:

1. Molecularly targeted prescription to decrease toxicity and/or increase efficacy:
   – EGFR
   – TGFá
   – Cyclin D
   – Hypermethylation
   – p16, p53
   – Telomerase
2. New multicenter administrative model
   – Translational focus
   – Multidisciplinary, multicenter
   – Animal models

STEPHEN PIANTADOSI, Johns Hopkins University
Clinical Trial Design and Statistical Issues

Many preventive or therapeutic interventions are available for testing. Most issues pertaining to dose-safety relationships are resolved during translational and early development efforts, and the discussion below therefore focuses on design considerations in middle development. The conceptual steps in middle development center on addressing the question of whether the intervention is safe and effective enough to warrant continued evaluation in expensive, comparative trials. The outcomes in middle development include safety, surrogate, and definitive outcomes. No surrogates are possible for safety; safety is simply a measure of the observed rates of complications. Surrogate markers include pathologic grade, tumor shrinkage, or tumor response. Choices for the definitive outcome are cancer incidence and survival, from diagnosis of cancer or a premalignant condition. A good surrogate outcome should be: in the causal pathway for disease process; strongly correlated to outcome; evident relatively soon after treatment (otherwise no savings from measuring surrogate *versus* definitive outcome); and easily and reliably measured. The defining characteristic, and the central point of failure, is that the surrogate must respond to treatment in the same manner as the definitive outcome [161]. Of concern is that putative surrogate outcomes may suggest a beneficial treatment effect, but the outcome may be neutral or reversed when the definitive study is done (*e.g.*, Cardiac Arrhythmia Suppression Trial). The commonly used surrogate of tumor shrinkage may also correlate poorly, or not at all, with cancer progression or survival.

BE offers several advantages as a prevention model. BE is not an uncommon condition, and is relatively easy to diagnose. BE provides a good example of premalignant changes with high risk for cancer, and the tissue is accessible for diagnosis and longitudinal study. Disadvantages of BE include the possibility that genotypic variability will engender different outcomes. Relatively long latency with respect to

duration of developmental trials is also of concern. Surrogate outcomes would require validation; use of dysplasia grade as a surrogate is hampered by the subjectivity of pathological interpretation, and the challenge of how to quantitatively assess the response. However, the overriding limitation is the low frequency of definitive events.

Design options in middle development include using an immediate outcome or treatment effect (*e.g.*, tumor shrinkage) and an external standard (*e.g.*, historical data) to decide if a more expensive comparative trial is warranted. Alternatively, the decision could be based on a delayed treatment effect (*e.g.*, tumor stasis or prevention) and an external standard. Another option is to randomize a population to two or more treatments with the goal of picking the winner. The best performer would be taken forward to a comparative clinical trial where one of the arms then would be a standard therapy, the so-called randomized Phase II design.

Factorial designs may have particular application in cancer prevention. These designs simultaneously test more than one treatment and are applicable in two seemingly paradoxical cases: when it is important and necessary to learn about interactions between treatments and when interactions are known not to be present. To implement the two-by-two factorial design, it must be possible to simultaneously administer both treatments (*i.e.*, no overlapping toxicities) and ethically acceptable to use a placebo (or neither treatment) group. An important consideration is that the interactions tend to be scale (model) dependent; thus, the same data might alternatively show no *versus* a negative interaction, depending on whether an additive or multiplicative scale is employed. Notable examples of the factorial design include the Physician's Health Study and the ATBC Prevention Trial.

Crossover trials lend themselves greatly to efficiency. The primary efficiency stems from the use of the same patient group for both treatments. The treatment effect is based upon within-patient rather than between-patient comparisons, resulting in increased precision and reduced variability. The potential for a positive correlation between a given patient's performance on either treatment also enhances efficiency. However, it is theoretically possible that outcomes will be negatively correlated, and a significantly powerful interaction could swamp the beneficial effect of the savings in sample size. Additional advantages of the crossover design include improved recruitment. The disadvantages deserve serious consideration. A primary concern is the carry-over effect. Compared with an independent group design, drop-outs are doubly consequential and analysis is more complex. Additionally, regulators may not favorably regard this design.

Therapeutic and prevention trials in BE are subject to the typical pitfalls of middle and late development, particularly inadequate infrastructure to support the trial. A second problem concerns retroactive definitions, which can reconstruct the selection bias that careful eligibility screening was designed to avoid. Imprecision in estimated treatment effect may arise from small sample size, or incomplete accrual. Invalid surrogate outcomes also pose a significant problem. Two areas of development are needed to support clinical trials of any nature in BE. The first is cooperative multicenter collaboration; the accrual resources will not be found at any one institution. Second is

development of reliable surrogate biomarkers or clinical outcomes for BE. The decision to further investigate treatments is dependent on the certainty that the short-term surrogates being employed are in fact representative of definitive outcomes for the disease. Accessibility of the lesion, particularly its longitudinal accessibility, is very attractive for prevention studies and the infrastructure to support trials in BE should take advantage of this.

Recommendations:

1. Cooperative, multicenter collaboration
2. Development of reliable surrogates - biomarkers and/or clinical

GROUP DISCUSSION AND RECOMMENDATIONS

Discussion Leader: Ernie Hawk

The following issues were discussed:

1. Surveillance trial
    - Endpoint:
        - Cancer is the most clinically meaningful endpoint
        - High-grade dysplasia is also a key outcome, but dysplasia is continuum
    - Explore surveillance interval
    - Analogous to National Polyp Study
    - Would establish standardized surveillance of BE (interval, biopsy protocol, *etc.*)
    - Would permit biomarker validation
    - Natural history is difficult to discern because interventions are common (high-grade dysplasia is often removed, treated, or sampled)
    - Technological and other developments during course of trial could make the study obsolete
    - Large, long trial is only mechanism for addressing the impact of surveillance

2. Intervention Trial
    - High-grade dysplasia:
        - Endoscopic ablation +/- pharmacologic intervention *versus* surgery (cannot be randomized)
        - Endoscopic ablation *versus* pharmacologic intervention (in patients unfit for surgery)
    - Low-grade dysplasia with additional risk factors:
        - Phase II molecularly-targeted pharmacologic interventions
            - Pick-the-winner approach would eliminate need for placebo in early efficacy evaluation
            - Large, simple follow-up trial could evaluate best performer

3. Screening study
    - New technologies (*e.g.*, transnasal endoscope) could be assessed in pilot study

- Population
  - Should include asymptomatic individuals
  - Colonoscopy cohort?
- Significant potential for public health impact
- Biomarker assessment (serum, blood)
- Justification is questionable: no recommended intervention once BE cohort is identified; how will adenocarcinoma be prevented?
- Technological and other developments during course of trial could make the study obsolete
- Large, long trial is only mechanism for investigating issues such as risk factors, etiology, prevalence
- Would feed surveillance trial

4. Mechanism to tie centers together (multidisciplinary network)
   - Existing Cooperative Group system will not address need
   - Each component of network brings different, complementary expertise
   - Would facilitate expedient clinical translation of nonclinical leads
   - Multidisciplinary approach is essential to take advantage of unique opportunity to study carcinogenic process afforded by accessibility of BE tissue
   - Biomarker endpoints:
     - Not enough known at present
     - "Validated": predictive in prospective cancer endpoint studies
     - Tissue banks needed
     - Exploration of new approaches (molecular signatures, expression arrays, and cytology) would benefit from basic science input
     - Centralized pathology with molecular characterization
   - Establish cohort from which clinical studies can be conducted
     - BE registry (Internet-based, nationwide)
     - Scale (thousands of patients) is feasible in BE with multicenter approach
   - Support personnel (*e.g.*, for biopsy suite)
   - Data management
     - Standardized questionnaires
     - Common Data Elements

Recommendations:

1. Establish a multicenter, multidisciplinary collaborative network among experts in BE to facilitate screening, surveillance and intervention studies. This network would provide a shared infrastructure for central pathology, endpoint definition, data management, and the development of common data elements and standardized questionnaires.
2. Conduct a surveillance trial to establish the natural history and clinical management of BE.
3. Conduct an intervention trial to evaluate the efficacy of ablative, surgical and molecularly-targeted pharmacological strategies in BE.

4. Employ a minimally-invasive technology to conduct a screening study in asymptomatic and symptomatic populations to establish the risk factors and etiology of BE.

APPENDIX A: BARRETT'S ESOPHAGUS WORKING GROUP ROSTER

Extramural Experts:
Marcia Canto MD, MHS - Johns Hopkins University
Donald Castell MD - Medical College of Pennsylvania
Glenn Eisen MD, MPH - Vanderbilt University
Arlene Forastiere MD - Johns Hopkins University
Raj Goyal MD - Harvard University
Charles Lightdale MD - Columbia University
Stephen Meltzer MD - University of Maryland
Stephen Piantadosi MD, PhD - Johns Hopkins University
Dawn Provenzale MD, MS - Duke University
Brian Reid MD PhD - University of Washington
Richard Sampliner MD - University of Arizona
Prateek Sharma MD - University of Kansas
Jon Stuart Spechler MD - University of Texas, Southwestern
Jacques Van Dam MD, PhD - Stanford University
Thomas Vaughan MD, MPH - University of Washington
Kenneth K. Wang MD - Mayo Foundation

NIH Participants:
William Anderson MD, MPH - NCI/DCP
Wong-Ho Chow PhD - NCI/DCEG
Barbara Conley MD - NCI/DCTD
Sandy Dawsey MD - NCI/CCR
James Everhart MD - NIDDK
Joseph F. Fraumeni, Jr. MD - NCI/DCEG
Peter Greenwald MD, DrPH - NCI/DCP
Kate Z. Guyton PhD - CCS Associates
Frank Hamilton MD - NIDDK
Ernest Hawk MD, MPH - NCI/DCP
Jay Hoofnagle MD - NIDDK
Stephen James MD - NIDDK
Richard Kaplan MD - NCI/DCTD
Richard Klausner MD - NCI/OD
Leslie Ford MD - NCI/DCP
Sandra Melnick DrPH, MPH - NCI/DCCPS
Lori Minasian MD - NCI/DCP
Alan Rabson MD - NCI/OD
Ellen Richmond MS - NCI/DCP
Patricia Robuck PhD, MPH - NIDDK
Allen Spiegel MD - NIDDK
Edward Staab MD - NCI/DCTD
Daniel Sullivan MD - NCI/DCTD
Jaye L. Viner MD - NCI/DCP

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