Esophageal cancer poses an interesting challenge for oncologists. Esophageal squamous cell cancer has the most varied geographical incidence of any cancer, suggesting the existence of critically important environmental and molecular epidemiologic factors. These factors remain largely unrecognized.

Equally puzzling is the dramatic increase in the incidence of adenocarcinomas of the esophagus and gastro-esophageal junction or cardia that has occurred in western societies during the past 3 decades.[1,2] This increase in incidence is particularly disturbing in view of the highly lethal nature of esophageal cancer. For the year 2000, the estimated number of new cases of esophageal cancer in the United States is 12,300 and the estimated number of deaths due to this cancer is 12,100.[3] In response to these challenges, there has been a great increase in the amount of research and the number of publications on malignant and premalignant esophageal diseases. In the 2-week period following January 26, 2000, for example, 136 new English language entries using any of the key words [esophageal neoplasms, Barrett's esophagus, gastric cardia, and gastro-esophageal reflux] were added on Medline. Many readers of Oncology are thus likely to welcome the efforts by Forastiere et al to review this increasing mass of information.

**Barrett’s Esophagus and Esophageal Adenocarcinoma**

The main risk factor for esophageal adenocarcinoma is the presence of Barrett’s esophagus. This is currently defined by most investigators as the replacement of the normal squamous epithelium of the distal esophagus by a visible segment of columnar mucosa containing intestinal metaplasia on microscopic examination.

Similar to adenocarcinoma, the incidence of Barrett’s esophagus has been rising rapidly,[4,5] suggesting that the increase in esophageal adenocarcinoma incidence is explained, at least in part, by this increase in Barrett’s. However, another possible explanation is that the proportion of patients with Barrett’s who progress to malignancy has increased. The latter explanation is not supported by recent prospective analyses of the risk of cancer developing in patients with Barrett’s,[6,7] but large population-based studies are needed to properly evaluate this possibility.

It may be that the incidence of nonvisible intestinal metaplasia, termed either [ultra-short segment Barrett’s esophagus] or [cardiac mucosa with intestinal metaplasia] is increasing. Indeed, recent studies have found intestinal metaplasia at the gastroesophageal junction in 9% to 36% of individuals undergoing endoscopy.[8-10] The normal-appearing gastroesophageal junction was rarely studied prior to the mid-1990s. Consequently, a rise in intestinal metaplasia at this site cannot be confirmed. It has been hypothesized that the increasing incidence of adenocarcinoma at the gastroesophageal junction or cardia is a consequence of this putative increase in the incidence of nonvisible areas of intestinal metaplasia.

As Forastiere et al note, there is considerable variability in the reported risk of developing adenocarcinoma within a segment of Barrett’s esophagus. In part, this reflects the fact that none of the reported prospective studies has included sufficient numbers of patients to make definitive estimates, and that the size of a study required to provide these estimates is prohibitively large. Furthermore, because only a small proportion of Barrett’s mucosa is usually biopsied at endoscopy, there is considerable risk that patients with Barrett’s are staged incorrectly for the presence and grade of dysplasia, thus confounding estimates of the cancer risk in supposedly nondysplastic Barrett’s epithelium. Even when Barrett’s segments are carefully evaluated histologically, with a large number of biopsies taken throughout the Barrett’s segment, conventional examination of the
biopsy specimens using histopathologic techniques may be insufficient to stratify patients according
to cancer risk. This is because areas of esophageal mucosa that are similar histologically can be very
different genetically.

Studies at our institution have found that molecular differences are particularly marked if either
adenocarcinoma or dysplasia is present within the esophagus, even if adenocarcinoma or dysplasia
is not present in the biopsy sample.[11-13] Thus, it is likely that individual patients with Barrett’s
esophagus will eventually need to be staged for risk of disease progression by a combination of
molecular and conventional pathologic methods (molecular pathology), and that the risk of
malignant degeneration in populations with Barrett’s esophagus will need to be investigated using
the tools of molecular epidemiology.

**GERD and Esophageal Adenocarcinoma**

In both studies that addressed this question, gastroesophageal reflux disease (GERD), as identified
by symptoms of that disease, was found to be a significant risk factor for esophageal
adenocarcinoma.[14,15] As Forastiere et al note, Lagergren et al found that the strength of the
association with reflux symptoms was very similar in esophageal adenocarcinoma patients in whom
Barrett’s esophagus was and was not detected.[15]

This finding has been interpreted by Lagergren et al, and by Forastiere et al in this review, to
indicate that reflux has an effect on the development of esophageal adenocarcinoma that is
independent of Barrett’s esophagus, and that gastroesophageal reflux, rather than Barrett’s
esophagus may be the crucial factor in causing esophageal adenocarcinoma.[15] This controversial
statement has been dismissed by some commentators because of the likelihood of tumor
overgrowth of the Barrett’s segment and the risk of sampling error. Without Barrett’s columnar
metaplasia as an intermediate step, it is difficult to explain how adenocarcinoma can develop from
squamous epithelium.

Nevertheless, the findings of Lagergren et al and similar findings by others compel us to consider
alternative mechanisms of tumor development. One possibility is that a renegade cell and its
clonal progeny may progress to malignancy without significant clonal expansion in terms of the
surface area of the esophagus involved.

Alternatively, the traditional thinking that goblet cells are required for cancer risk may be incorrect.
Indeed, our observations suggest that goblet cells are progressively lost in the sequence of
progression from Barrett’s metaplasia to dysplasia to adenocarcinoma. It may be that, if sufficient
genetic alterations are present, cancer can arise in some cases from columnar metaplasia without
goblet cells.

**Antireflux Surgery**

Forastiere et al fail to include antireflux surgery among the available treatments for GERD in their
discussion of acid peptic disorders. Although in their subsequent review of cancer prevention, they
note the ability of surgical fundoplication to prevent esophageal exposure to both acid and duodenal
alkaline reflux, no details or references are provided. In view of the large number of studies that
have confirmed the effectiveness of antireflux surgery for GERD, this omission is an oversight.

Both the two randomized trials[16,17] and two nonrandomized trials[18,19] that compared medical
and surgical therapy for GERD found significant advantages for surgical treatment. Furthermore, a
prospective, randomized comparison of medical and surgical therapy in patients with Barrett’s
esophagus showed that both treatments provided good symptom control, but the medically treated
patients had a higher prevalence of post-treatment persistent esophagitis (53%) and stricture (45%)
than did the operated group (esophagitis, 5%; stricture, 15%). Dysplasia developed in 6 (22%) of 27
patients during medical treatment but in only 1 (3%) of 32 patients after antireflux surgery.[20] In
the surgical patient who developed dysplasia, pH monitoring revealed that fundoplication had been
ineffective.[20]

Similarly, an analysis of patients with Barrett’s esophagus in the American College of
Gastroenterology registry indicated that dysplasia developed in 19.7% of patients treated medically
but in only 3.4% of those treated surgically.[21] Our group reported that complete regression of
visible segments of intestinal metaplasia was very unusual after antireflux surgery (as it is with
medical therapy), but that complete regression of microscopic-only intestinal metaplasia at the
gastroesophageal junction occurred in 73% of patients.[22]

Interestingly, in the population-based study by Lagergren et al discussed above, patients who used
medications to relieve symptoms of reflux for at least 5 years before being interviewed had a greater
risk of esophageal adenocarcinoma than did individuals who were matched for severity of symptoms
but did not use such medications (odds ratio, 2.9; 95% confidence interval [CI], 1.9 to 4.6). Antireflux
surgery, in contrast, was not associated with an increased risk of adenocarcinoma of the
esophagus.[15]
Mechanisms by which acid suppressant medications may adversely affect the risk of developing esophageal adenocarcinoma are discussed elsewhere.[23] Large, randomized studies are needed to further investigate the significance of this trend toward the superiority of surgical treatment. Until the results of those trials are available, however, we believe that the published data justify regarding a properly performed antireflux operation as the gold standard therapy for reflux disease and for Barrett's esophagus with intestinal metaplasia or low-grade dysplasia.

**Mucosal Endoscopic Ablation**

For patients in whom low-grade dysplasia fails to regress after antireflux surgery, consideration of post-fundoplication mucosal endoscopic ablation[24] may be appropriate. Forastiere et al review the use of mucosal ablation in patients who have adenocarcinoma or Barrett's esophagus with high-grade dysplasia. As they note, significant complications (including the presence of submucosal foci of cancer after treatment) can follow these mucosal ablation procedures. These procedures remain experimental, and it is important that physicians, and the patients to whom they are offered, are aware of their limitations.

Mucosal endoscopic ablation is being used in patients with early cancers that are confined to the esophageal wall, with no apparent lymph node spread. Unfortunately, it is impossible to be certain of the lymph node status of these patients. Currently available staging methods, including endoscopic ultrasound, cannot accurately detect the presence of lymph node metastases in many patients. In our experience, 41% of patients with tumors confined to the esophageal wall will have lymph node involvement.[25] The fact that some patients with locoregional disease, including lymph node metastases, are cured after surgery alone indicates that selection of involved lymph nodes in patients without distant metastases can be beneficial. This benefit is not obtained with mucosal ablation techniques.

The appropriateness of mucosal ablation for treating high-grade dysplasia can also be questioned. Previously undetected cancers are present in the resected esophagus in almost 50% of patients undergoing esophagectomy for high-grade dysplasia.[26] The 5-year survival rate for these patients after esophagectomy is 90%.[27]

Thus, esophagectomy in patients with high-grade dysplasia is not the most aggressive form of prevention, as Heath et al. state; rather, it is the most prudent therapy, preventing cancer in half of patients and curing this usually incurable cancer in 90% of the others. We believe that it is more aggressive to use an experimental procedure in patients who could expect a high cure rate if treated by standard methods. If mucosal ablation techniques are to be used in patients with cancer and high-grade dysplasia, this should be done only in the context of a randomized, controlled trial.

**Esophageal Adenocarcinoma in Patients With Achalasia**

Although Forastiere et al correctly state that there is no known association between achalasia and esophageal adenocarcinoma, it is worth noting that Barrett's esophagus and esophageal adenocarcinomas can occur in patients with achalasia. In these patients, severe GERD has developed after iatrogenic disruption of the lower esophageal sphincter, with the impaired clearance of refluxed material by the aperistaltic esophageal body no doubt a contributing factor.[28] For this and other reasons, we advocate laparoscopic Heller's myotomy with partial fundoplication for the treatment for achalasia.

**Chemoprevention**

As Forastiere et al note, there is considerable interest in developing rational chemoprevention strategies to prevent the development of adenocarcinoma in patients with Barrett's esophagus. One of the most promising approaches involves inhibition of cyclooxygenase 2 (COX-2) expression using COX inhibitors, such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), or selective COX-2 inhibitors, such as celecoxib (Celebrex) and rofecoxib (Vioxx). Cyclooxygenase-2 activity has been implicated as an important factor in tumorigenesis in general, and COX-2 is involved in a large number of processes fundamental to tumor development.

As reviewed by Forastiere et al, three epidemiologic studies have shown that use of aspirin or NSAID is associated with a significantly lower risk of either developing, or of dying from, esophageal cancer, including esophageal adenocarcinoma. Importantly, several groups have shown that expression levels of COX-2 are elevated in patients with Barrett's esophagus and esophageal adenocarcinoma.[12,29,30] These results suggest that Barrett's intestinal metaplasia and low-grade dysplasia lesions are suitable tissues for chemoprevention trials using COX inhibitors.[31] Forastiere et al also discuss the use of retinoids for chemoprevention in patients with Barrett's esophagus. Although a phase II trial of 13-cis-retinoic acid (isotretinoin [Accutane]) in patients with Barrett's esophagus found no early evidence of regression of Barrett's esophagus, this trial included
only 16 patients studied for 6 weeks.[32]
The effectiveness of retinoid therapy can be influenced by the expression patterns of the retinoic acid receptors. Retinoic acid receptor (RAR) messenger RNA (mRNA) expression levels are altered in both Barrett's and esophageal adenocarcinoma tissues, with significant upregulation of retinoic acid receptor-alpha (RAR-alpha) and significant downregulation of retinoic acid receptor-gamma (RAR-gamma).[13]
These findings may be helpful in designing future retinoid chemoprevention trials for patients with Barrett's esophagus. One interesting chemoprevention approach for Barrett's would be to combine retinoids and COX-2 inhibitors. The rationale for this (possibly synergistic[33]) approach is that COX-2 transcription can be suppressed by retinoids.[34]

**References:**


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