TABLE 109-2 SOME ETIOLOGIC FACTORS ASSOCIATED WITH ADENOCARCINOMA OF THE ESOPHAGUS

Chronic gastroesophageal reflux
Obesity
Barrett's esophagus
Male sex
Cigarette smoking

hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris) have each been linked with squamous cell esophageal cancer, as have dietary deficiencies of molybdenum, zinc, selenium, and vitamin A. Patients with head and neck cancer are at increased risk of squamous cell cancer of the esophagus.

For unclear reasons, the incidence of squamous cell esophageal cancer has decreased somewhat in both the black and white populations in the United States over the past 40 years, whereas the rate of adenocarcinoma has risen sevenfold, particularly in white males (male-to-female ratio of 6:1). Whereas squamous cell cancers comprised the vast majority of esophageal cancers in the United States as recently as 40–50 years ago, more than 75% of esophageal tumors are now adenocarcinomas, with the incidence of this histologic subtype continuing to increase rapidly. Understanding the cause for this increase is the focus of current investigation.

Several strong etiologic associations have been observed to account for the development of adenocarcinoma of the esophagus (Table 109-2). Such tumors arise in the distal esophagus in association with chronic gastric reflux, often in the presence of Barrett's esophagus (replacement of the normal squamous epithelium of the distal esophagus by columnar mucosa), which occurs more commonly in obese individuals. Adenocarcinomas arise within dysplastic columnar epithelium in the distal esophagus. Even before frank neoplasia is detectable, aneuploidy and *p53* mutations are found in the dysplastic epithelium. These adenocarcinomas behave clinically like gastric adenocarcinomas, although they are not associated with *Helicobacter pylori* infections. Approximately 15% of esophageal adenocarcinomas overexpress the *HER2/neu* gene.

CLINICAL FEATURES

About 5% of esophageal cancers occur in the upper third of the esophagus (cervical esophagus), 20% in the middle third, and 75% in the lower third. Squamous cell carcinomas and adenocarcinomas cannot be distinguished radiographically or endoscopically.

Progressive dysphagia and weight loss of short duration are the initial symptoms in the vast majority of patients. Dysphagia initially occurs with solid foods and gradually progresses to include semisolids and liquids. By the time these symptoms develop, the disease is already very advanced, because difficulty in swallowing does not occur until >60% of the esophageal circumference is infiltrated with cancer. Dysphagia may be associated with pain on swallowing (odynophagia), pain radiating to the chest and/or back, regurgitation or vomiting, and aspiration pneumonia. The disease most commonly spreads to adjacent and supraclavicular lymph nodes, liver, lungs, pleura, and bone. Tracheoesophageal fistulas may develop, primarily in patients with upper and mid-esophageal tumors. As with other squamous cell carcinomas, hypercalcemia may occur in the absence of osseous metastases, probably from parathormone-related peptide secreted by tumor cells (Chap. 121).

DIAGNOSIS

Attempts at endoscopic and cytologic screening for carcinoma in patients with Barrett's esophagus, while effective as a means of detecting high-grade dysplasia, have not yet been shown to reduce the likelihood of death from esophageal adenocarcinoma. Esophagoscopy should be performed in all patients suspected of having an esophageal abnormality, to both visualize and identify a tumor and also to obtain histopathologic confirmation of the diagnosis. Because the population of persons at risk for squamous cell carcinoma of the esophagus (i.e., smokers and drinkers) also has a high rate of cancers of the lung and the head and neck region, endoscopic inspection of the larynx, trachea, and bronchi should also be carried out. A thorough examination of the fundus of the stomach (by retroflexing the endoscope) is imperative as well. The extent of tumor spread to the mediastinum and para-aortic lymph nodes should be assessed by computed tomography (CT) scans of the chest and abdomen and by endoscopic ultrasound. Positron emission tomography scanning provides a useful assessment of the presence of distant metastatic disease, offering accurate information regarding spread to mediastinal lymph nodes, which can be helpful in defining radiation therapy fields. Such scans, when performed sequentially, appear to provide a means of making an early assessment of responsiveness to preoperative chemotherapy.

TREATMENT ESOPHAGEAL CANCER

The prognosis for patients with esophageal carcinoma is poor. Approximately 10% of patients survive 5 years after the diagnosis; thus, management focuses on symptom control. Surgical resection of all gross tumor (i.e., total resection) is feasible in only 45% of cases, with residual tumor cells frequently present at the resection margins. Such esophagectomies have been associated with a postoperative mortality rate of approximately 5% due to anastomotic fistulas, subphrenic abscesses, and cardiopulmonary complications. Although debate regarding the comparative benefits of transthoracic versus transhiatal resections has continued, experienced thoracic surgeons are now favoring minimally invasive transthoracic esophagectomies. Endoscopic resections of superficial squamous cell cancers or adenocarcinomas are being examined but have not yet been shown to result in a similar likelihood of survival as observed with conventional surgical procedures. Similarly, the value of endoscopic ablation of dysplastic lesions in an area of Barrett's esophagus on reducing subsequent mortality from esophageal carcinoma is uncertain. Some experts have advocated fundoplication surgery (i.e., the removal of the gastroesophageal junction) as a means of cancer prevention in patients with Barrett's esophagus; again, objective data are not yet available to fully assess the risks versus benefits of this invasive procedure. About 20% of patients who survive a total surgical resection live for 5 years. The evaluation of chemotherapeutic agents in patients with esophageal carcinoma has been hampered by ambiguity in the definition of "response" and the debilitated physical condition of many treated individuals, particularly those with squamous cell cancers. Nonetheless, significant reductions in the size of measurable tumor masses have been reported in 15–25% of patients given single-agent treatment and in 30–60% of patients treated with drug combinations that include cisplatin. In the small subset of patients whose tumors overexpress the *HER2/neu* gene, the addition of the monoclonal antibody trastuzumab (Herceptin) appears to further enhance the likelihood of benefit, particularly in patients with gastroesophageal lesions. The use of the antiangiogenic agent bevacizumab (Avastin) seems to be of limited value in the setting of esophageal cancer. Combination chemotherapy and radiation therapy as the initial therapeutic approach, either alone or followed by an attempt at operative resection, seems to be beneficial. When administered along with radiation therapy, chemotherapy produces a better survival outcome than radiation therapy alone. The use of preoperative chemotherapy and radiation therapy followed by esophageal resection appears to prolong survival compared with surgery alone according to several randomized trials and a meta-analysis; some reports suggest that no additional benefit accrues when surgery is added if significant shrinkage of tumor has been achieved by the chemoradiation combination.

For the incurable, surgically unresectable patient with esophageal cancer, dysphagia, malnutrition, and the management of tracheoesophageal fistulas are major issues. Approaches to palliation include repeated endoscopic dilatation, the surgical placement of a gastrostomy or jejunostomy for hydration and feeding, endoscopic placement of an expansive metal stent to bypass the tumor, and radiation therapy.