2 Endoscopic Screening for Squamous Cell Carcinoma of the Esophagus

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CONTENTS

1. INTRODUCTION

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

2. RATIONALE FOR SCREENING

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

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3. HIGH-RISK ASSOCIATIONS

3.1. RACE, GENDER, AND GEOGRAPHIC ASSOCIATIONS

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

Table 1
Conditions or Exposures Strongly Associated With Esophageal SCC

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

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

3.2. CHRONIC TOBACCO AND ALCOHOL USE

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

3.3. PREVIOUS SCC OF THE UPPER AERODIGESTIVE TRACT

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

3.4. DIETARY FACTORS AND POOR SOCIOECONOMIC STATUS

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

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

3.5. CAUSTIC INGESTION

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

3.6. ACHALASIA

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

3.7. TYLOSIS (DIFFUSE PALMOPLANTAR KERATODERMA)

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

3.8. RADIATION THERAPY TO THE CHEST

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

3.9. LICHEN PLANUS

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

4. METHODS FOR IMPROVING THE ENDOSCOPIC DETECTION OF DYSPLASIA

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

4.1. MAGNIFICATION ENDOSCOPY

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

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

4.2. CHROMOENDOSCOPY

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

4.3. SPECTROSCOPY AND OPTICAL COHERENCE TOMOGRAPHY

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

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

5. EFFECTIVENESS OF SCREENING

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

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

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

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

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

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

6. CONCLUSIONS AND RECOMMENDATIONS

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

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

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

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