Squamous Dysplasia—The Precursor Lesion for Esophageal Squamous Cell Carcinoma

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Abstract

Esophageal squamous cell carcinoma (ESCC) accounts for 80% of all esophageal cancers worldwide, and esophageal squamous dysplasia (ESD) is the only histopathology that predicts the development of ESCC. The prevalence of ESD parallels rates of invasive ESCC and is typically found in 25% or more of adults above the age of 35 years in populations in north central China, where risk for ESCC is among the highest in the world. Results of chemoprevention and early detection studies to prevent progression of ESD suggest that these approaches, coupled with emerging endoscopic therapies, offer promise for the prevention of esophageal cancer mortality in high-risk populations. Future research on ESD and ESCC should focus on finding additional modifiable risk factors and on identifying biomarkers to incorporate into early detection strategies. *Cancer Epidemiol Biomarkers Prev; 22(4); 540–52. ©2013 AACR.*

Introduction and Historical Context

Rates

Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer-related death in the world, with an estimated 482,000 new cases and 407,000 deaths in 2008 (1). There are 2 main histopathologic types of esophageal cancer, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). EAC, due largely to gastroesophageal reflux disease and obesity, has increased dramatically in the past 30+ years and is now the predominant type in the United States and most other Western countries. Worldwide, however, ESCC dominates with 80% of all cases, due largely to high rates in many developing countries. China, with its high rates and large population, accounts for over half of all esophageal cancer–related deaths in the world and nearly all are ESCC. High rates of esophageal cancer are found along geographic belts, one following the ancient Silk Road from north central China through the central Asian republics to northern Iran, and one from eastern to southern Africa (Fig. 1). This minireview will focus only on precursors of ESCC.

Precursors

Although early studies conducted in high-risk areas suggested that esophagitis was a precursor for ESCC (2), subsequent studies have shown that dysplasia is the only histopathology that predicts the development of ESCC. Qiu and Yang (3) were the first to provide evidence that esophagitis alone was nonspecific and dysplasia was a precancerous state, but the most definitive assessment of risk from squamous esophageal histology has come from follow-up of 682 participants in the Linxian Dysplasia Nutrition Intervention Trial (NIT), who participated in an endoscopy survey in 1987 (4). A comparison of initial biopsy diagnoses with the occurrence of ESCC over the subsequent 3.5 years showed that only dysplasia predicted development of ESCC and that increasing grades of dysplasia predicted increased risk: compared with normal, relative risks [95% confidence intervals (CI)] were 2.2 (0.7–7.5) for mild dysplasia, 15.8 (5.9–42.2) for moderate dysplasia, 72.6 (29.8–176.9) for severe dysplasia, 22.9 (6.7–78.0) for dysplasia not otherwise specified, and 62.5 (24.1–161.9) for carcinoma *in situ* (CIS). Of note, dysplasia not otherwise specified (NOS) and moderate dysplasia risks were similar, as were risks for carcinoma *in situ* and severe dysplasia. Further follow-up of this same endoscopic cohort for a total of 13.5 years corroborated the previous risk estimates and provided more precise quantification. Over the full follow-up period, ESCC developed in 8% of participants with normal histology but 24% with mild dysplasia, 50% with moderate dysplasia, 74% with severe dysplasia, 58% with dysplasia NOS, and 75% with carcinoma *in situ* (Fig. 2; ref. 5).

Histologic and Molecular Characterization

Histologic characterization

Histologic criteria for the ESCC precursor lesion, esophageal squamous dysplasia (ESD), were initially described in the 1970s (6–9) and modified in the 1980s based on experience in China (10). Squamous dysplasia requires the presence of nuclear atypia (enlargement, pleomorphism, and hyperchromasia), loss of normal cell polarity, and abnormal tissue maturation without invasion of epithelial cells through the basement membrane. Compared

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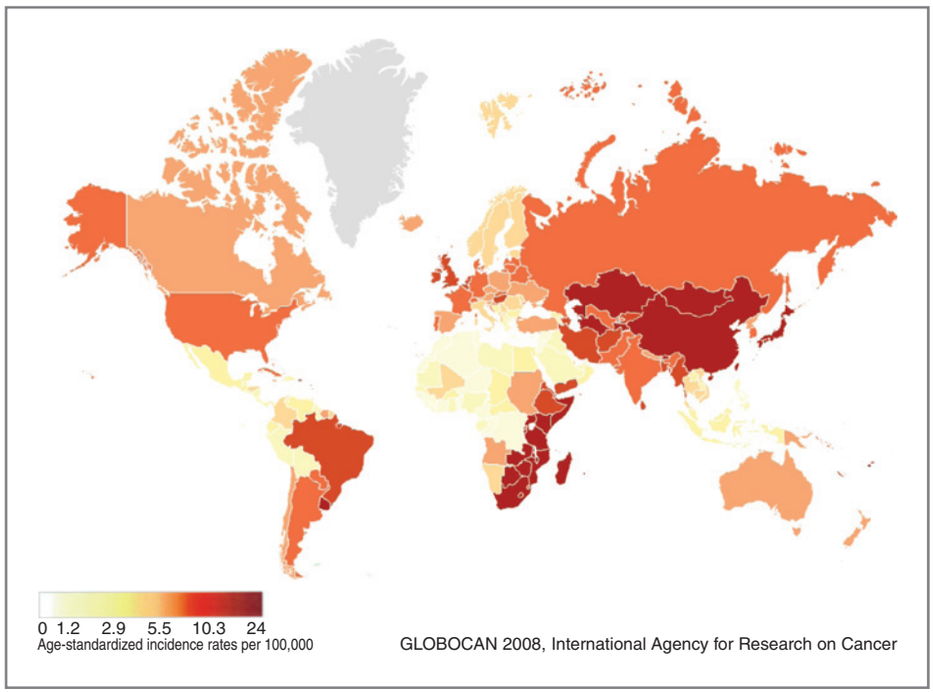

Figure 1. Esophageal cancer incidence worldwide in 2008 (men).

with normal (Fig. 3A), in mild dysplasia these abnormalities are confined to the lower third of the epithelium (Fig. 3B), whereas in moderate dysplasia they are present in the lower two thirds of the epithelium (Fig. 3C), and in severe dysplasia they also involve the upper third of the epithelium (Fig. 3D). Full thickness involvement of the epithelium, called carcinoma *in situ* by some, is considered synonymous with severe dysplasia based on their similar histologic appearance and risk of progression to invasive ESCC. A final category, dysplasia NOS, indicates that dysplasia is present but cannot be graded accurately because of poor tissue orientation or artifact and has progression risk approximating that of moderate dysplasia; rebiopsy to accurately grade the dysplasia would be necessary to define cancer risk.

Molecular characterization

Numerous molecular alterations in ESCC tumors have been identified. Among them, *TP53* alterations are the most common. One study of 56 ESCC cases from north central China found at least 1 genetic alteration in *TP53* in 96% of the tumors studied, including mutations (77%), allelic loss within the gene (73%), and/or LOH at the TP53 microsatellite marker (80%); and three quarters of the cases had 2 or more such alterations (11). In a study conducted in northeastern Iran, 90% of the 119 ESCC

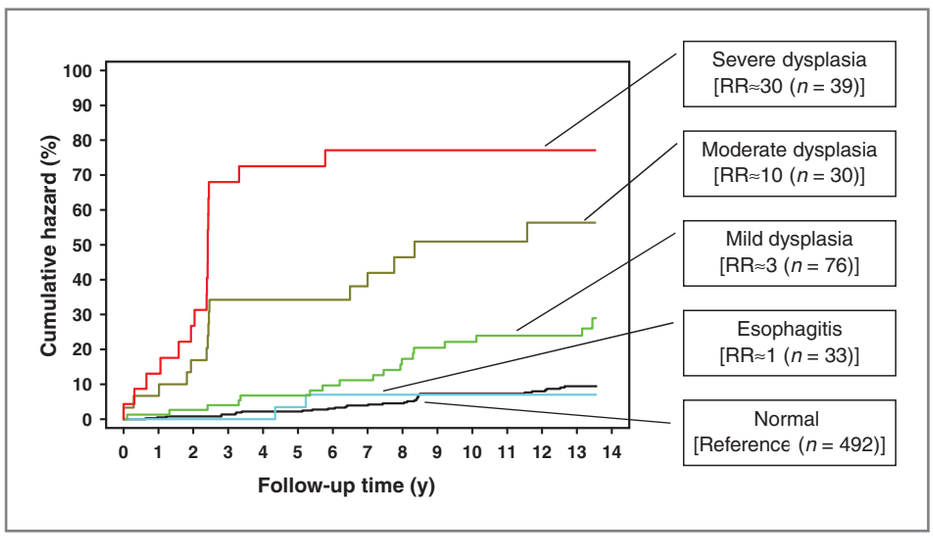

Figure 2. ESCC precursor lesions: cumulative incidences and relative risks for the development of ESCC over 13.5 years of follow-up by initial histology ($N = 670$).

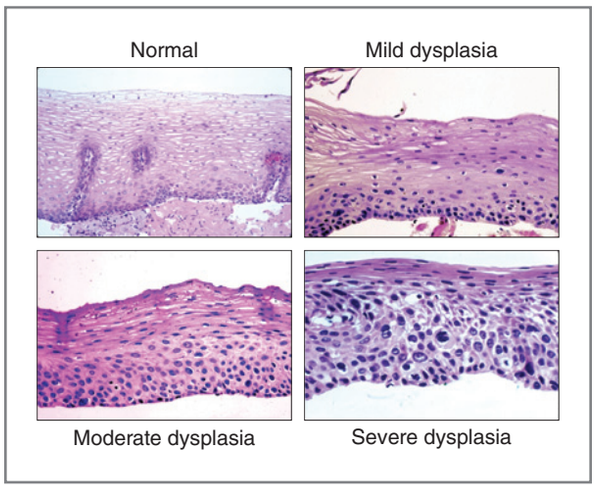

Figure 3. Histologic appearance of normal squamous epithelial and mild, moderate, and severe esophageal squamous dysplasia.

cases evaluated had a *TP53* mutation, including 11 with 2 or 3 mutations (12). The *TP53* mutation pattern observed in this study was heterogeneous, in a manner suggestive of environmental exposures. Typical hotspots were only infrequently mutated, whereas 40% of altered bases were at mutagenesis sites known to be associated with polycyclic aromatic hydrocarbon exposure, and the mutation patterns differed by the reported temperature of the tea consumed. Another study of 60 ESCCs from north central China observed at least 1 alteration in *p16INK4a* in 68% of cases (50% aberrant methylation, 17% microsatellite LOH) and at least 1 alteration in *p15INK4b* in 50% (35% homozygous deletion, 47% microsatellite LOH, 18% aberrant methylation; ref. 13). In addition, RNA array expression studies have found numerous other dysregulated genes as gain- and loss-of-function candidates in ESCC (14). Recently, whole-exome sequencing found that ESCCs had an average of 83 mutations per tumor, and that the most frequent mutations in ESCC occurred in *TP53* (92% of the 12 cases sequenced), *NOTCH1* (33%), *NOTCH3* (25%), and *FBXW7* (17%; ref. 15).

Premalignant lesions of the squamous esophagus have been studied much less than ESCC tumors. The most common molecular-oriented approach applied to premalignant lesions thus far has been immunohistochemical studies of the expression of 1 or more candidate proteins. Numerous studies have shown overexpression of p53 protein in squamous dysplasia compared with normal tissue. In one study, for example, 92% of 12 dysplasia samples and 0% of 14 normal tissue samples obtained from the resection specimens of 44 ESCC cases were p53 positive, as were all 5 dysplasia biopsies and 50% of 6 normal biopsies taken from 51 cancer-free patients (16). Other proteins shown to have increased expression in dysplasia include CD44 (17); TGF-β I (positive in 81% of dysplasia vs. 37% of normal samples; ref. 18); PCNA (positive in 75% of dysplasia vs. 55% of normal; refs. 19, 20); FADD, CDC25B, fascin, CK14, LAMC2, and SPARC (21); p16 (positive in 88% of dysplasia vs. 10% of normal), p15 (positive in 73% of dysplasia vs. 0% in normal), p14 (positive in 100% of dysplasia vs. 15% of normal; ref. 22); and PTCH1 (positive in 21% of dysplasia vs. 0% of normal; ref. 23). Decreased expression in dysplasia compared with normal has been observed for TGF-β receptor II (81% positive in dysplasia vs. 98% positive in normal; ref. 18); esophagin (positive in 9% of dysplasia vs. 53% of normal; ref. 20); and Fas, caspase-8, CK4, annexin 1 (21).

Nucleic acid–based studies of precursors have shown increased allelic loss (pointing to potential tumor suppressor gene inactivation sites) with increasing grade of dysplasia at a wide variety of microsatellite loci (i.e., 3p, 4p, 5q, 8p, 9p, 9q, 10p, 11p, 13q, and 17p; refs. 24–27). Mutation studies in esophageal squamous precursors have been limited to *TP53*, where missense mutations were evident early in esophageal carcinogenesis (4 of 11 samples with dysplasia vs. 1 of 3 normal epithelia; ref. 28). Several studies have evaluated promoter hypermethylation in candidate genes in esophageal precursors (29–32). Most of these studies showed little or no hypermethylation in normal tissue, with progressively more hypermethylation as morphology advanced toward ESCC. Of the 30+ different genes evaluated, only *p16INK4a* was examined in all 4 studies, and it showed hypermethylation in from 4% to 38% of lesions with dysplasia.

While a reasonable number of studies have reported molecular characteristics in esophageal squamous premalignancy, these studies often used different designs and analytic approaches, few studies examined the same targets, objective and quantitative assessments were not typical, and sample sizes were generally small. Taken together, these differences limit the comparability and overall conclusions that can be drawn from the studies.

More recently, high throughput genome-wide methods in the analysis of patterns of RNA expression (33–35), differential methylation, and gene copy number have shown promise in distinguishing patients with and without high-grade squamous dysplasia (36). Real progress in identifying the changes driving esophageal squamous carcinogenesis will require the comprehensive application of new high throughput technologies, including whole-genome sequencing, RNA sequencing, and global epigenomics, in addition to objective, quantified characterization of protein expression, all analyzed in a fully integrated manner.

Genetic susceptibility to ESCC is evidenced by the identification of tylosis, a rare autosomal dominant skin disorder characterized by hyperkeratosis of the palms and soles reported in the literature in 3 families (37), and recent findings from genome-wide association studies (GWAS), where up to 17 loci have been associated with ESCC risk in Chinese populations (38–41). While cumulative risk of ESCC to age 70 years in family members with tylosis is estimated at more than 90%, risk associated with alleles identified in GWAS to date is modest (e.g., the per allele

OR for *PLCE1* is 1.34). Experience with breast cancer suggests that even the combination of all GWAS hits together is unlikely to demonstrably improve clinical risk prediction (42). There are, as yet, no published studies on the genetics or genomics of susceptibility to ESD.

Descriptive Epidemiology and Etiology

Etiology of ESCC

While all ESCCs share a common histology, etiologically there are 2 distinctly different ESCC diseases. ESCC occurs in developed countries at rates that are low to moderate, and etiology there can be attributed almost entirely to exposure to alcohol and tobacco (43). In contrast, in the economically less developed countries in eastern and central Asia and eastern and southern Africa, where rates of ESCC are the highest in the world, alcohol and tobacco exposure have little or no role. The Taihang Mountain region of north central China has the highest ESCC incidence in China, with rates in women that are nearly as high as in men despite the fact that very few women use tobacco or drink alcohol (44, 45). Similarly, northern Iran has high rates, yet alcohol is consumed by less than 2% of the population due to religious proscription (46). Studies in high-risk regions suggest that exposure to carcinogens such as polycyclic aromatic hydrocarbons (47), opium (46), poor nutrition (48–52), and thermal damage (45, 53) are major risks, whereas tobacco exposure plays only a minor role (44–46). Despite these differences in etiology, both high- and low-rate ESCC share dysplasia as their precursor lesion, and thus approaches to screening and treatment are common to both.

Prevalence of precursor lesions

The prevalence of esophageal squamous dysplasia has been documented best in the areas of the world where ESCC rates are highest, specifically in Iran and China, where reports from 11 surveys have been published (Table 1). Dysplasia prevalence has varied from 3% to 38% in these surveys, due in part to differences in the populations (i.e., risk level, age and gender differences, whether or not persons had a prior diagnosis of dysplasia, and the presence of symptoms), endoscopy methods (i.e., use of Lugol's iodine on the mucosa, number of biopsies taken), and the pathology criteria used (2, 3, 10, 54–59). The earliest surveys found lower rates, most likely due to different pathology criteria and lack of mucosal iodine staining. The 2 surveys from Iran both found 4% prevalence (54, 59), whereas with rare exception, the Taihang Mountain region in China has shown dysplasia prevalences that were much higher, exceeding 20%.

The 5 most recent surveys in north central China reported grades of dysplasia in addition to total dysplasia prevalence (10, 55–58). In these surveys, the most common grade of dysplasia was mild (median, 10.6%; range, 2.6%–14.0%), followed by moderate (7.8%, 0.2%–12.0%), and severe (including CIS; 5.3%, 0.4%–7.4%).

Risk factors for dysplasia

The few studies conducted to evaluate risk factors for esophageal squamous dysplasia have all been conducted in the high-risk Taihang Mountain region in China. These studies have focused on known or suspected risk factors for cancer and have not included wide-ranging assessments of risk for esophageal squamous dysplasia associated with other exposures.

A screening study of 724 healthy adults of ages 40 to 65 years from Linxian conducted in 2002 (57) served as the basis for 4 evaluations of risk factors for dysplasia. Among the 720 subjects who underwent endoscopy during this study, the prevalence of risk factors among the 230 subjects with dysplasia was compared with the prevalence among 490 subjects without dysplasia. Questionnaire-based analyses found significantly increased risk for dysplasia among persons who had a positive family history of cancer (OR, 1.57; 95% CI, 1.13–2.18), had higher systolic blood pressure (1.11/10 mm Hg, 1.03–1.19), used a heating stove without a chimney (2.22, 1.27–3.86) and had lost more but not all of their teeth (1.91 for 12–31 vs. <4 teeth lost, 1.17–3.15). Although not quite statististically significant, risk of dysplasia was lower in households with smaller size and higher income (60). Higher serum 25-hydroxyvitamin D concentrations were also associated with increased risk for dysplasia in this endoscopy cohort (OR, 1.86; 95% CI, 1.35–2.62 for high vs. low quartile; ref. 61). Serum pepsinogens (PG) I and II were evaluated in 125 dysplasia cases and 250 sex-matched controls from this same cohort. In this study, PG I levels did not differ between dysplasia cases and noncases, however, the PG I/II ratio showed a strong dose–response relation, with lower PG I/II levels associated with increased risk of dysplasia (OR, 2.12; 95% CI, 1.08–4.18 for low vs. high quartile), consistent with a role for gastric atrophy in the etiology of esophageal dysplasia (62). Finally, the association between HPV and ESCC has been inconsistent (63–68). In precursors, 1 study of HPV DNA in esophageal cells from balloon cytology found no association with dysplasia (69), whereas 2 other studies did observe HPV DNA in dysplasia (70, 71).

An endoscopic survey from Anyang among 7,381 inhabitants evaluated questionnaire-based exposure to tobacco, alcohol, tooth loss, pesticide exposure, preferred food temperature, and water source as potential risk factors in 228 cases (97.5% with dysplasia, 2.5% with ESCC) compared with 6,932 control subjects without ESCC or dysplasia (58). Among these 6 potential risk factors, only water source showed a significant association with dysplasia/ESCC. Subjects with deep wells had lower risk of dysplasia/ESCC than persons with shallow wells (OR, 0.72; 95% CI, 0.54–0.96).

A summary comparison of risk factors evaluated for both ESCC and dysplasia is shown in Table 2. With the exceptions of smoking (a risk for ESCC but not dysplasia) and serum pepsinogens (a risk for dysplasia but not ESCC), the other risk factors studied were concordant for both dysplasia and ESCC.

Table 1. Prevalence of ESCC precursor lesions

			Population				EGD[a]	Dysplasia						
Year reported	Authors (ref no.)	Location	Number	Age, y	Gender	Prior dysplasia	Mucosal iodine	Mild	Moderate	Severe	CIS	All dysplasia	Invasive ESCC	All dysplasia by gender
1979	Crespi and colleagues (54)	Gonbad, Iran	430	15–70	M+F	None	No	NA[b]	NA	NA	NA	4%	NA	5% M, 3% F
1982	Munoz and colleagues (2)	Linxian, PRC	527	25–55+	M+F	One-third	No	NA	NA	NA	NA	8%	0.9%	8% M, 8% F
1988	Qiu and Yang (3)	Linxian and Boaixian, PRC	1,043	NA	M+F	Most	No	NA	NA	NA	NA	17%	1.8%	17% M, 18% F
1988	Qiu and Yang (3)	Huixian, PRC	300	35–65	M+F	NA	No	NA	NA	NA	NA	38%	2.7%	37% M, 41% F
		Fanxian, PRC	300	35–65	M+F	NA	NA	NA	NA	NA	NA	5%	1.0%	6% M, 4% F
1994	Dawsey and colleagues (10)	Linxian, PRC	754	40–69	M+F	All	No	10.6%	4.6%	5.8%	1.6%	23%	4.6%	
1997	Roth and colleagues (55)	Linxian, PRC	439	50–69	M+F	None	Yes	12.0%	10.0%	6.0%	NA	28%	4.0%	
2004	Lu and colleagues (56)	Cixian, PRC	2,013	40–69	M+F	NA	Yes	8.6%	7.8%	2.6%	2.7%	22%	0.7%	26% M, 18% F
2008	Pan and colleagues (57)	Linxian, PRC	725	50–64	M+F	NA	Yes	14.0%	12.0%	5.0%	NA	32%	0.6%	
2010	He and colleagues (58)	Anyang, PRC	7,381	25–65	M+F	NA	Yes	2.6%	0.2%	0.2%	0.2%	3%	0.1%	
2012	Etemadi and colleagues (59)	Gonbad, Iran	724	NA	M+F	None	Yes	NA	NA	NA	NA	4%	NA	

[a]EGD, esophagogastroduodenoscopy.
[b]NA, information not available.

Table 2. Comparison of risk factors evaluated for ESCC and esophageal squamous dysplasia in China

Risk factor	ESCC (Ref. no.)	Dysplasia (Linxian) (Ref. no.)	Dysplasia (Anyang) (Ref. no.)
Gender	No (44)	No (60)	No (58)
Tobacco smoking	Yes (44, 45)	No (60)	No (58)
Alcohol drinking	No (44, 45)	No (60)	No (58)
Family history of cancer	Yes (44)	Yes (60)	NA[a]
Tooth loss	Yes[b]	Yes (60)	No (58)
Serum vitamin D	Yes[c]	Yes (61)	NA
Water source	Yes (44)	NA	Yes (58)
Serum pepsinogens	No[d]	Yes (62)	NA
Hot liquids/food	No (44) and yes (45)	NA	No (58)
HPV	No (65–67) and yes (63–64, 68, 70, 71)	No (69) and yes (70, 71)	Yes (63)

[a]NA, information not available.

[b]Abnet CC, Qiao Y-L, Mark SD, et al. Prospective study of tooth loss and incident esophageal and gastric cancers in China. Cancer Causes Control 2001;12(9):847–54.

[c]Chen W, Dawsey SM, Qiao Y-L, et al. Prospective study of serum 25(OH)-Vitamin D concentration and risk of esophageal and gastric cancer. Br J Cancer 2007;97(1):123–8.

[d]Ren JS, Kamangar F, Qiao YL, et al. Serum pepsinogens and risk of gastric and oesophageal cancers in the General Population Nutrition Intervention Trial cohort. Gut 2009;58(5):636–42.

Clinical Perspective and Natural History

Survival

The survival of ESCC is very poor, largely due to late development of symptoms and consequent late diagnosis. The most recent 5-year relative survival rate for esophageal cancer in the Surveillance Epidemiology and End Results (SEER) registries (2001–2007) was 19% (72). In developing countries, however, where most of the ESCC cases occur, survival rates are much lower. A recent study from northeastern Iran reported a 5-year survival rate of 3.4% (73), which is probably a more typical figure in high-risk, low-resource populations.

Survival is dramatically dependent on the stage of disease at diagnosis: in SEER (2001–2007), the 5-year survival rates were 37%, 18%, and 3% for localized, regional, and distant disease, and in China, 5-year survival of patients with stage T1 ESCC has been reported to be 86% (74).

The large difference in survival by stage suggests that early detection of precursor lesions and early-stage cancers might offer a chance to significantly reduce mortality. The problem, of course, is how to identify individuals with these early treatable lesions, as virtually all of these people are asymptomatic. Thus, the challenge is to risk-stratify asymptomatic people and then develop an accurate, patient-acceptable, and cost-effective way to screen high-risk groups and find the few individuals who need treatment.

Endoscopic visualization of dysplasia

One way to identify ESD and early ESCC is by endoscopy with Lugol's iodine staining. Iodine reversibly binds with glycogen, which is abundant in the superficial cells of normal esophageal squamous mucosa but is scant or absent in the rapidly dividing cells of significant esophagitis or dysplasia. Thus, spraying Lugol's iodine solution on the esophageal mucosa turns normal areas brown but leaves areas of severe esophagitis or dysplasia unstained. These negative image "unstained lesions" (USLs) can be endoscopically targeted for biopsy and, if appropriate, focal endoscopic therapy (Fig. 4). The sensitivity of these USLs for the presence of high-grade (moderate or severe) ESD or early invasive ESCC is very high, around 95% in studies from China (75, 76), and the specificity (around 65%) is greatly improved after the biopsies are read, distinguishing between esophagitis and dysplasia.

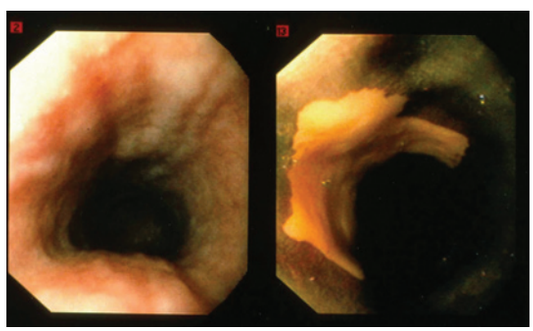

Figure 4. Esophageal squamous dysplasia without and with Lugol's iodine staining. An unstained lesion becomes readily apparent after topical application of Lugol's iodine solution which can then be targeted for biopsy.

Natural history of dysplasia

The natural history of ESD has not been extensively studied, but some observations bearing on the progression of these lesions have been reported. As noted earlier, follow-up of untreated patients in a high-risk Chinese population with biopsy-proven mild, moderate, and severe squamous dysplasia showed development of clinically diagnosed ESCC in 5%, 27%, and 65% after 3.5 years (4) and 24%, 50%, and 74% after 13.5 years (5). Another report of patients with moderate or severe dysplasia who were followed endoscopically for 16 months found that 22% with moderate dysplasia and 60% with severe dysplasia showed endoscopic (size) or histologic progression during this period (77). No similar follow-up studies of untreated patients with ESD have been reported from Western populations. Thus, at least in China, ESD seems to progress over months to many years, depending on the grade. But based on the high cumulative incidence figures reported above, it is probable that severe dysplasia needs prompt treatment, moderate dysplasia needs treatment or periodic endoscopic follow-up, and mild dysplasia can be followed at longer intervals. There is a need for more studies evaluating the natural history of ESD, and a need for consensus clinical guidelines for treatment and patient follow-up after treating these lesions.

Treatment of dysplasia

Several endoscopic methods are used to treat ESD. Excisional methods, in which the lesion is excised endoscopically, include endoscopic mucosal resection (EMR) using the "cap method" (78), EMR using the "banding method" (also called multiband mucosectomy, or MBM; ref. 79), and endoscopic submucosal dissection (78, 80). Ablative methods, which burn the lesions *in situ*, include multipolar electocoagulation (MPEC), argon plasma coagulation (APC), and radiofrequency ablation (RFA; ref. 76). An advantage of the excisional methods is the preservation of the lesion in a surgical specimen, which can be reviewed pathologically to document the true extent of disease and evaluate the need for additional therapy, but a disadvantage is that they require greater endoscopic expertise to perform. All of these treatment methods are relatively new in high-risk areas, so the optimal clinical follow-up protocols are still being defined and the procedural costs and cost–benefit comparisons are still being evaluated.

Prospects and Implications for Prevention

Target and strategy

Dysplasia, the ESCC precursor lesion, is a target for prevention strategies, including both chemoprevention and screening, even though there is not yet a strategy in place.

Chemoprevention

Chemoprevention emerged as a cancer prevention strategy in the 1980s, and ESCC was a target for prevention in 2 early nutrition intervention trials conducted in China. Results from those trials showed that supplementation with the combination of selenium/vitamin E/β-carotene reduced total mortality, total cancer mortality, and gastric cancer mortality and incidence in the Linxian General Population NIT, but no benefit was seen for esophageal cancer (48). No effect was seen on esophageal cancer incidence or mortality from multivitamin supplementation in the Linxian Dysplasia NIT (81). The beneficial effects of selenium/vitamin E/β-carotene on mortality were still evident up to 10 years after the cessation of supplementation in the Linxian General Population NIT, and reduced esophageal cancer mortality was also seen then among younger participants (82).

There have been many more trials evaluating precursor and precursor-related lesions of the squamous esophagus than there have been trials with actual cancer endpoints. As with the cancer endpoint-based prevention trials, these precursor trials have all been conducted in northern China. A total of 13 analyses (summarized in Table 3) have been published from 10 different interventions (83–94). All but 2 of the trials evaluated a nutritional intervention, including a variety of micronutrients (e.g., retinol, riboflavin, zinc, calcium, selenium, multivitamins, etc.), decaffeinated green tea, and freeze-dried strawberries, whereas a single trial evaluated antitumor B (a mixture of 6 Chinese herbs) and a retinoid (95), and another tested celecoxib (92). Trial endpoints were typically histologic or cytologic regression or progression, or prevalence of dysplasia, with a few reports of other intermediate endpoint markers (e.g., prevalence of micronuclei or proliferation markers). Evidence for a beneficial effect on premalignancy was observed in 4 of these studies: the combination of retinol+riboflavin+zinc reduced micronuclei (84); multivitamins improved cytology (90); selenomethionine improved histology (92); and strawberries improved histology and reduced proliferation and expression of several cancer-related proteins (94). A benefit for cancer was observed for antitumor B (85) and riboflavin (85) and was suggested among persons whose communities received riboflavin-fortified salt (93).

Use of screening

The determination that ESD is the preneoplastic lesion for ESCC provides the possibility of screening not just for early stage ESCC, but also to screen for and treat the preneoplastic lesion itself in a manner analogous to screening and treating cervical dysplasia to prevent cervical cancer. A comprehensive system that uses chromoendoscopy and grade-specific therapy for ESD has the potential to reduce disease incidence and disease-specific mortality. In areas with very high rates of the disease it could even reduce total mortality. A community assignment trial in a high-incidence region of China has shown that endoscopic screening and treatment reduced esophageal cancer incidence and mortality (Unpublished Data). But like all screening methodologies, the use of this regimen remains speculative without confirmatory randomized trial data that prove that this method is beneficial,

Table 3. Chemoprevention trials evaluating precursor and precursor-related lesions of the squamous esophagus in north China

Year reported	Authors (Ref. no.)	Location	Population	Design	Intervention	Duration	Endpoint(s)	Result
1985	Munoz and colleagues (83)	Huixian	$N = 610$ 35–64 y	2-Arm RCT[a]	Retinol+riboflavin+zinc (vs. placebo)	13.5 mo	Esophagitis (histo)	No effect
1987	Munoz and colleagues (84)	Huixian	$N = 200$ 35–64 y	2-Arm RCT	Retinol+riboflavin+zinc (vs. placebo)	13.5 mo	Micronuclei in esophageal cells (histo)	Benefit (Intervention 0.19% vs. placebo 0.31%)
1988	Lin and colleagues (85)	Heshun, Linxian	$N = 1{,}728$ severe dysplasia	3-Arm RCT	Antitumor B, Retinamide (vs. placebo)	3 y	Cytology regress/ progress	No effect for antitumor B[b] No effect for retinamide[b]
1988	Lin and colleagues (85)	Heshun, Linxian	$N = 2{,}412$ mild dysplasia	2-Arm RCT	Riboflavin (vs. placebo)	3 y	Cytology regress/ progress	No effect[c]
1993	Wang and colleagues (86)	Huixian	$N = 200$ non-normal 30–60+ y	2-Arm RCT	Calcium (vs. placebo)	11 mo	Histology regress/ progress	No effect on histology
							Proliferation	No effect on proliferation
1994	Wang and colleagues (87)	Linxian	$N = 391$ 40–69 y	2×4 Fractional factorial RCT	4 Micronutrient groups/factors	5.25 y	Dysplasia/ cancer (histo)	No effect for any of 4 factors
1994	Dawsey and colleagues (88)	Linxian	$N = 833$ and 396 dysplasia 40–69 y	2-Arm RCT	Multivitamins (vs. placebo)	2.5 and 6 y	Dysplasia/cancer (histo)	No effect at either time point
1994	Rao and colleagues (89)	Linxian	$N = 512$ dysplasia 40–69 y	2-Arm RCT	Multivitamins (vs. placebo)	2.5 y	Proliferation (histo)	No effect overall
1994	Mark and colleagues (90)	Linxian	$N = 3{,}318$ dysplasia 40–69 y	2-Arm RCT	Multivitamins (vs. placebo)	2.5 and 6 y	Cytology regress/ progress	Benefit (Intervention OR for regression to nondysplasia = 1.23)
2002	Wang and colleagues (91)	Huixian	$N = 200$ non-normal 30–60+ y	2-Arm RCT	Decaffeinated green tea (vs. placebo)	12 mo	Histology regress/ progress	No effect
2005	Limburg and colleagues (92)	Linxian	$N = 238$ dysplasia 34–68 y	2×2 Factorial RCT	Selenomethionine, Celecoxib	11 mo	Histology regress/ progress	Benefit in mild dysplasia (Selenomethionine increased regression & decreased progression ≈2-fold each)

(Continued on the following page)

Table 3. Chemoprevention trials evaluating precursor and precursor-related lesions of the squamous esophagus in north China (Cont'd)

Year reported	Authors (Ref. no.)	Location	Population	Design	Intervention	Duration	Endpoint(s)	Result
2009	He and colleagues (93)	Cixian	$N = 9$ townships (11,392 persons) fortified vs. 12 townships (10,711 persons) unfortified	Endoscopy comparison of 950 fortified vs. 1,300 unfortified group persons 40–69 y (randomly selected)	Riboflavin-fortified salt (vs. unfortified salt)	6 y	Dysplasia (histo) Cancer (histo)	No effect on dysplasiaSuggested benefit for cancer (Intervention 1.6% vs. placebo 3.1%)
2011	Chen and colleagues (94)	Henan, Shandong	$N = 75$ dysplasia	37 low dose, 38 high dose (randomized to dose group)	Freeze-dried strawberries (low, high doses)	6 mo	Histology regress/progress Proliferation Protein expression	Benefit for high dose (reduced histology grade in 81%) Benefit for high dose (reduced Ki-67 labeling by 38%) Benefit for high dose (reduced iNOS 80%, COX-2 63%, NF-κB-p65 63%, pS6 73%)

[a]RCT, randomized controlled trial.

[b]Neither antitumor B nor retinamide improved cytology regression/progression overrall, but antitumor B reduced the number of new cancers (3.9% for antitumor B group vs. 8.3% for placebo group).

[c]Riboflavin did not improve cytology regression/progression overall but reduced the number of new cancers (1.7% for riboflavin group vs. 2.1% for placebo group).

because there is clear evidence that early detection of cancer is not always beneficial because not all preneoplastic lesions progress and treatments may cause serious complications and side effects (96).

Furthermore, populations with high incidence rates of esophageal cancer tend to be poor and medically underserved. Endoscopic screening and treatment of an entire population would be expensive and would require many highly trained physicians and expensive equipment. Risk stratification to reduce the number of people needing screening would be useful, but this remains impractical based on demographic and easily collected exposure variables (59, 60). Alternatively, a simpler primary screening test that identifies subjects most likely to be positive for ESD could reduce the number of individuals needing endoscopic screening. Previous attempts to use balloon cytology (analogous to a Pap smear) to find subjects with ESD showed that this method was likely too insensitive and nonspecific to be useful for full-scale screening (55, 57). But improved molecular testing of nonendoscopically retrieved esophageal cells has shown promise for screening for the EAC precursor, Barrett's esophagus (97), and may facilitate ESD screening as well.

Summary

ESCC is the predominant form of esophageal cancer worldwide, particularly in developing countries, and has among the poorest survival of all cancers. ESD is the precursor lesion for ESCC and the prevalence of ESD is 25% or more among adults in areas of north central China where ESCC rates are highest. Risk factors for ESD seem largely to parallel those of invasive ESCC. The high prevalence of ESD in high-risk areas, coupled with simple but sensitive endoscopic-based methods to detect dysplasia, suggest that early detection of persons with precursor lesions for subsequent prevention strategies such as chemoprevention or endoscopic therapy offer substantial promise for the reduction of ESCC mortality. Future research on ESD and ESCC should focus on finding additional modifiable risk factors and on identifying biomarkers to incorporate into patient-acceptable early detection strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.R. Taylor, C.C. Abnet, S.M. Dawsey
Development of methodology: P.R. Taylor, S.M. Dawsey
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.R. Taylor, S.M. Dawsey
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.R. Taylor, C.C. Abnet, S.M. Dawsey
Writing, review, and/or revision of the manuscript: P.R. Taylor, C.C. Abnet, S.M. Dawsey
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.R. Taylor
Study supervision: P.R. Taylor, S.M. Dawsey

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