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Review Article

Secondary Prevention of Esophageal Squamous Cell Carcinoma in Areas Where Smoking, Alcohol, and Betel Quid Chewing are Prevalent

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Esophageal cancer is ranked as the sixth most common cause of cancer death worldwide and has a substantial effect on public health. In contrast to adenocarcinoma arising from Barrett's esophagus in Western countries, the major disease phenotype in the Asia–Pacific region is esophageal squamous cell carcinoma which is attributed to the prevalence of smoking, alcohol, and betel quid chewing. Despite a multidisciplinary approach to treating esophageal cancer, the outcome remains poor. Moreover, field cancerization reveals that esophageal squamous cell carcinoma is closely linked with the development of head and neck cancers that further sub-optimize the treatment of patients. Therefore, preventive strategies are of paramount importance to improve the prognosis of this dismal disease. Since obstacles exist for primary prevention via risk factor elimination, the current rationale for esophageal cancer prevention is to identify high-risk groups at earlier stages of the disease, and encourage them to get a confirmatory diagnosis, prompt treatment, and intensive surveillance for secondary prevention. Novel biomarkers for identifying specific at-risk populations are under extensive investigation. Advances in image-enhanced endoscopy do not just substantially improve our ability to identify small precancerous or cancerous foci, but can also accurately predict their invasiveness. Research input from the basic sciences should be translated into preventive measures in order to decrease the disease burden of esophageal cancer.

Key Words: areca nut, betel quid, cancer prevention, esophageal cancer, image-enhanced endoscopy

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Disease Burden of Esophageal Squamous Cell Carcinoma

In parallel with the increase of metabolic disorders, gastroesophageal reflux disease and its complications have become one of the most prevalent diseases globally.[1,2] However, in contrast with esophageal adenocarcinoma arising from Barrett's esophagus in Western countries, the major disease phenotype in the Asia–Pacific region is esophageal squamous cell carcinoma (ESCC).[3] In Taiwan, the standardized death rate for esophageal cancer increased from 3.6 (5.9 in males) to 5.0 (9.3 in males) per 100,000 population in the period 1992 to 2008, and this disease currently ranks as the ninth leading cause of cancer deaths.[4] The most susceptible age for esophageal cancer has decreased. In 2008, the median age of death was 58 years for males, which is a 7-year decrease compared with that of 1998.[4] If we combine oral cancer, hypopharyngeal cancer, and esophageal cancer into a single disease category, it may be the second most common cancer in men in Taiwan and is increasing at a rapid rate. Collectively, the distinct epidemiologic characteristics of esophageal cancer to Western countries suggest strategies to prevent esophageal cancer are crucial and must be tailored to the needs of this region.

Primary Prevention of Esophageal Cancer

Risk factors for ESCC include carcinogen exposure, hot tea drinking, chronic mucosal irritation, a family history of malignancy, and pre-existing tumors of the aero-digestive tract.[3] Also, lower body mass index, lower educational level, and poorer socioeconomic status were found in patients with esophageal cancer.[5] Among protective factors are citrus fruits and yellow and green vegetables, which contain vitamin C and β-carotene.[6] In a Japanese study, an increase in consumption of total vegetables and fruit by 100 grams per day was associated with an 11% decrease in the risk of esophageal cancer.[6] Coffee consumption and some medications, such as angiotensin-converting enzyme inhibitors, aspirin, and non-steroidal anti-inflammatory drugs, might protect against esophageal cancer.[7,8]

Abstinence from smoking, alcohol ingestion, and betel quid chewing is mandated for cancer prevention. Many case-control studies have confirmed their carcinogenic effects (Table 1).[9–29] Smoking [odds ratio (OR) = 1.6–16.9; summarized OR = 2.6, 95% confidence interval (CI) = 2.4–2.9], alcohol consumption [OR = 1.1–17.6; summarized OR = 2.7, 95% CI = 2.5–2.9], and betel quid chewing (OR = 1.6–9.4; summarized OR = 7.2, 95% CI = 4.5–11.3) increase the risk of esophageal cancer in a dose-dependent relationship as well as synergistic effects.[9–30] For instance, the concomitant use of alcohol and tobacco leads to a higher risk with an OR of 8 and further adding betel quid chewing can augment the OR to 195.6 (95% CI = 64.0–864.2).[19,25]

Focus on Betel Quid Chewing

Betel quid chewing is a common behavior in South and Southeast Asia.[3] In addition to its carcinogenic effect, betel quid chewing is associated with obesity, hypertriglyceridemia, hyperglycemia, metabolic syndrome, cardiovascular disease, hepatic dysfunction, cirrhosis of the liver and liver cancer.[31–33] Exposure of parents to betel nut may transgenerationally increase the risk of metabolic syndrome in their offspring.[34]

Biologically, the constituents of betel nuts may inhibit expression of the p53 tumor suppressor, impair DNA repair, and activate matrix metalloproteinases-2, -8, and -9, which may accelerate tumor migration.[35,36] Adding slaked lime can decrease the astringent taste of the raw betel fruit and chewing with Piper betel Linn can increase the refreshing taste, but both of these additives increase the risk of esophageal cancer.[21] Swallowing betel quid juice also increases the risk of esophageal cancer (OR = 3.3; 95% CI = 1.3–9.3).[25]

Table 1. Association between alcohol consumption, smoking, betel quid chewing and the risk of esophageal squamous cell carcinoma

Year/ location	Case/ control (*n*)	Alcohol* consumption	Smoking*	Betel quid chewing*	Reference
1981/US	120/250	6.4 (2.5–16.4)	1.3 (0.8–2.4)	–	Pottern et al [9]
1988/US	275/275	15.5 (5.9–41.1)[a]	11.5 (4.5–29.8)[b]	–	Yu et al [10]
1990/Uruguay	261/522	5.3 (2.7–10.2)[c]	4.6 (1.9–11.1)[d]	–	De Stefani et al [11]
1990/US	178/174	3.1 (1.7–5.7)[e]	2.1 (1.1–3.9)[f]	–	Graham et al [12]
1990/Italy	288/1272	6.0 (3.7–10.0)[g]	3.8 (2.2–6.6)	–	Franceschi et al [13]
1991/India	267/895	2.3 (1.5–3.6)	4.8 (2.3–9.8)[h]	–	Sankaranarayana et al [14]
1992/Hong Kong	400/1598	11.5 (5.7–19.7)[i]	5.8 (2.8–12.0)[j]	–	Cheng et al [15]
1994/China	902/1552	1.4	1.9	–	Gao et al [16]
1994/Argentina	131/262	2.9 (1.4–6.1)	2.9 (1.5–5.6)	–	Castelletto et al [17]
1995/US	106/724	9.5 (4.0–22.3)[k]	16.9 (4.1–69.1)[l]	–	Thomas et al [18]
1999/Argentina, Brazil, Paraguay, and Uruguay	830/1779	1.8 (1.2–2.6)	2 (1.4–2.8)	–	Castellsague et al [19]
2000/Sweden	167/820	1.1 (0.6–2.1)	9.3 (5.1–17.0)[m]	–	Lagergren et al [20]
2001/Taiwan	104/277	9.8 (4.2–22.6)[n]	3.7 (1.6–8.7)[o]	9.4 (1.8–48.3)[p]	Wu et al [21]
2003/Italy	395/1066	–	5.1 (3.3–7.7)[m]	–	Gallus et al [22]
2005/Taiwan	513/818	7.6 (5.2–11.1)[q]	4.2 (2.7–6.3)[m]	2.3 (1.4–3.7)[r]	Lee et al [23]
2005/Italy and Switzerland	805/3461	3.5 (1.1–10.8)[s]	8.8 (2.8–28.0)[m]	–	Garavello et al [24]
2006/Taiwan	165/255	17.6 (9.3–35.2)	5.4 (2.4–12.9)	1.7 (0.8–3.1)	Wu et al [25]
2007/Romania, Russia, Czech, and Poland	192/1114	2.86 (1.1–7.7)	7.4 (4.0–13.8)[m]	–	Hashibe et al [26]
2007/China	355/408	Male: 2.2 (1.5–3.2)/ Female: 0.8 (0.2–3.1)	Male: 2 (1.3–2.9)	–	Wang et al [27]
2008/Iran	300/571	–	1.63 (1.0–2.8)[m]	–	Nasrollahzadeh et al [28]
2008/Australia	303/1580	1.05 (1.04–1.07)	–	–	Pandeya et al [29]

**Data presented as odds ratios (95% confidence interval). The baseline comparators are: [a]alcohol < 120 g per day; [b]smoking < 3 packs per day; [c]alcohol < 250 g per day; [d]smoking < 25 cigarettes per day; [e]alcohol < 49 drinks per month; [f]smoking < 48 pack-years; [g]alcohol < 60 drinks per week; [h]smoking < 21 cigarettes per day; [i]alcohol < 1000 g per week; [j]smoking < 40 g per day; [k]alcohol < 21 drinks per week; [l]smoking < 80 pack-years; [m]never smokers; [n]alcohol < 1220 g-years; [o]smoking < 30 pack years; [p]betel quid < 495 betel years; [q]never drinkers; [r]never chewers; [s]alcohol < 49 drinks per week.*

Host Susceptibility to Esophageal Cancer

Males are more susceptible to this disease and prone to be at a more advanced stage when symptomatic.[27] Familial aggregation of this cancer is a well known phenomenon.[24] Genetic polymorphisms regulating folate metabolism are related to an increase of host susceptibility. Subjects with the methylenetetrahydrofolate reductase 677 TT genotype were found to be at higher risk (OR = 2.63, 95% CI = 1.75–3.94).[37] Also, the interleukin-6 (–174G > C) promoter gene polymorphism is associated with a higher risk (OR = 2.26, 95% CI = 1.37–3.73).[38]

Alcohol is metabolized to acetaldehyde by alcohol dehydrogenase (ADH) and the aldehyde

dehydrogenase (ALDH) converts acetaldehyde to acetate. Genetic polymorphisms encoding these two enzymes determine different rates of alcohol metabolism. A more rapid ethanol oxidation rate, such as occurs in subjects with more active ADH variants, and a slower acetaldehyde oxidation, such as occurs in subjects with less active ALDH variants, can lead to toxic accumulation of acetaldehyde, an alcohol flushing response, and a higher risk of esophageal cancer.[39] Studies from Yokoyama et al provided substantial evidence that alleles of alcohol and acetaldehyde metabolism genes modulate susceptibility to ESCC from alcohol consumption in Asian patients.[40] A recent European study also indicates that multiple ADH genes are associated with the risk of ESCC.[41]

Esophageal Cancer in Patients with Primary Head and Neck Cancer

Esophageal cancer can develop synchronously or metachronously in patients with head and neck cancers due to exposure to the same environmental carcinogens, which is one of the most important risk indicators.[42] Among head and neck cancers, patients with hypopharyngeal cancer have the highest risk for simultaneous esophageal cancer with a prevalence rate of 10–25%.[43] Thus routine examination of the esophagus has recently become a part of pre-treatment evaluation for newly diagnosed hypopharyngeal cancer.[43] In addition, metachronous esophageal cancer can develop in patients already treated for hypopharyngeal cancer with a relative risk of 12.4.[42] Thus endoscopic surveillance of the esophagus in patients with treated hypopharyngeal cancer also becomes an important issue.[44] Despite having a lower incidence of a second primary esophageal cancer than the incidence in hypopharyngeal cancer, patients with other head and neck cancers originating from the oral cavity, oropharynx, and larynx still have higher risks for esophageal cancer with relative risks of 1.5–8.6, 11.7, and 3.3 and absolute rates of 0.4–1.4%, 2.5%, and 0.5% per year, respectively.[42]

Secondary Prevention for Esophageal Cancer

The population with exposure history to tobacco, alcohol, and betel quid, and at risk for ESCC is so large that performing endoscopic screening for everyone may outnumber the capacity of endoscopists. Thus identification of high-risk subjects for second-stage confirmatory endoscopy is extremely important to optimize the utilization of medical resources. To this end, biomarkers with potential for accurately predicting cancer risk are essential for the achievement of secondary prevention (Table 2).[45–61]

Risk Stratification with Demographic Risk Factors

It is simple and practical to use demographic risk factors to triage individuals for endoscopy. Since the incidence of esophageal cancer increases with age, endoscopy has been proposed for patients over 40 years of age with alarming symptoms.[62] Wei et al proposed a predictive model for risk stratification in China.[48] In this multivariate model, more household members, a family history of cancer, higher systolic blood pressure, heating the home without a chimney, and having lost more but not all of their teeth were associated with a higher risk of having esophageal dysplasia. However, the sensitivity, specificity, and the area under the ROC curve were only 57%, 54%, and 58%, respectively.

Health Risk Appraisal Models

As mentioned previously, alleles of alcohol and acetaldehyde metabolism genes may modulate the risk of ESCC from alcohol drinking. Variations in blood acetaldehyde levels and facial flushing after alcohol are due to an inactive enzyme system encoded by the ALDH2*1/*2 genotype and have been associated with an increased risk of esophageal cancer.[63] Yokoyama et al, therefore, proposed the health risk appraisal (HRA) models

Table 2. Modalities for risk assessment of esophageal squamous cell carcinoma in high-risk populations

Year/location	Population	Screening modalities	Indicators	Reference
2003/Japan	65 ESCC men and 206 alcoholic male controls	Blood sampling and questionnaire	Higher MCV level and ALDH2 polymorphic genotype or alcohol flushing	Yokoyama et al [45]
2004/Hong Kong	31 HNSCC, 22 smokers, and 37 controls	Mouth and throat rinsing fluid cytology	DNA hypermethylation of *p15*	Chang et al [46]
2005/Iran	28 family members of ESCC, 30 sporadic ESCC, and 30 controls	Blood sampling	DNA hypermethylation of *p16*	Abbaszadegan et al [47]
2005/China	720 high-risk adults	Questionnaire, physical and dental examinations, and Lugol staining	Higher household members, cancer family history, higher systolic blood pressure, heating the home without a chimney, and having lost most but not all teeth	Wei et al [48]
2005/Brazil	182 high-risk men and 20 controls	Lugol staining	p53 protein expression	Fagundes et al [49]
2006/China	18 ESCC, 20 hyperplasia, 12 dysplasia, and 17 controls	Endoscopy	DNA hypermethylation of *MGMT*	Fang et al [50]
2006/China	6 ESCC and 18 controls	Esophageal balloon cytology or endoscopy	DNA hypermethylation of *p16, MGMT, RARbeta2, CLDN3, CRBP,* and *MT1G*	Roth et al [51]
2006/India	50 ESCC, 30 hyperplasia, 15 dysplasia, and 10 controls	Endoscopy	Loss of DAB2 protein expression	Anupam et al [52]
2006/China	69 ESCC, 39 LGD, 12 IGD, and 9 HGD	Endoscopy	DNA hypermethylation of *CDKN2A/p16 (INK4a), MGMT, E-cadherin*, and *RARbeta2*	Guo et al [53]
2007/Japan	542 asymptomatic adults	Lugol staining	*P53* gene alteration	Kaneko et al [54]
2007/Japan	56 ESCC and 42 controls	Lugol staining	DNA methylation and *p53* mutation	Ishii et al [55]
2007/China	13 early ESCC, 28 invasive ESCC, 85 hyperplasia, 44 esophagitis, and 91 controls	Blood sampling	Serum angiopoietin-2 level	Zhou et al [56]
2008/China	36 ESCC	Lugol staining	Loss of heterozygosity of D3S3644, D3S1768, D3S3040, D3S4542, RPL14, and D13S263	He et al [57]

(*Contd*)

2008/Japan	234 ESCC men and 634 male controls	Health risk appraisal model	ALDH2 polymorphic genotype or alcohol flushing, alcohol consumption, smoking, green-yellow vegetable and fruit consumption	Yokoyama et al [58]
2008/China	740 high-risk adults	Esophageal balloon cytology or Lugol staining	DNA hypermethylation of *AHRR*, *p16(INK4a)*, *MT1G*, and *CLDN3*	Adams et al [59]
2009/China	125 IGD-HGD and 250 controls	Blood sampling	Lower serum PGI/II ratio	Kamangar et al [60]
2009/Japan	404 cancer-free male controls	Health risk appraisal model + Lugol staining	The high detection rates for EPSCC in the top 10% risk group.	Yokoyama et al [61]

ESCC = Esophageal squamous cell carcinoma; MCV = mean corpuscular volume; ALDH = aldehyde dehydrogenase; HNSCC = head and neck squamous cell carcinoma; MGMT = O(6)-methylguanine-DNA methyltransferase; RARbeta2 = retinoic acid receptor beta2; CLDN = claudin; CRBP = cellular retinol-binding protein; MT1G = metallothionein 1G; DAB2 = disabled-2; CDKN2A = cyclin-dependent kinase inhibitor 2A; AHRR = aryl hydrocarbon receptor repressor; LGD = low-grade dysplasia; IGD = intermediate-grade dysplasia; HGD = high-grade dysplasia; PG = pepsinogen; EPSCC = esophageal/pharyngeal squamous cell carcinoma.

to triage the Japanese population.[58] Alcohol consumption, smoking, green-yellow vegetables and fruit intake, and the presence of facial flushing after alcohol (HRA-F) or the ALDH2 genotype (HRA-G) are included in the predictive models. Receiver operating characteristic curve analysis of the HRA-F model showed that when people in the top 10% of risk scores were selected for endoscopy, 57.9% of cancer cases were expected to be included (i.e. a sensitivity of 58%). The HRA-G model provided a slightly higher sensitivity of 65.4%. The area under the curve was 0.84 and 0.86 for HRA-F and HRA-G models, respectively. The same group validated these two HRA models in another Japanese population receiving mass screening and confirmed their ability to predict esophageal and pharyngeal cancers in the top 10% risk group.[61]

Serological Markers

Mean corpuscular volume was suggested as a convenient candidate biomarker to identify male drinkers with inactive ALDH2. A study from Japan has evaluated whether macrocytosis (i.e. an increase in mean corpuscular volume) is useful in the prediction of esophageal cancer.[45] With a cut-off value of 106 fL, the sensitivity and specificity were 43% and 83%, respectively. Even after adjusting for age, daily alcohol consumption, daily cigarette smoking, body mass index, and ADH2/ALDH2 genotypes, the cancer risk related to macrocytosis remained significant (OR = 2.75; 95% CI = 1.13–6.67). Gastric fundic atrophy may result in the reduction of gastric acid, proliferation of bacteria, and the production of carcinogens, such as acetaldehyde and nitrosamines.[64] Kamangar et al found that a lower serum pepsinogen I/II ratio was associated with an increased risk of esophageal cancer.[60] However, another study demonstrated that a lower pepsinogen I/II ratio was only associated with an elevated risk of gastric cancer but not esophageal cancer.[65] Serum angiopoietin-2 is a regulator of tumor angiogenesis and Zhou et al evaluated its ability to predict esophageal cancer.[56] In patients with invasive esophageal cancer, the

angiopoietin-2 levels were higher and the sensitivity of this marker for diagnosis was 78.6%. Nevertheless, the sensitivity was disappointingly 23.1% in the detection of superficial cancer.[56]

Molecular Markers Based on Biopsied Tissue

Genetic markers

Esophageal carcinogenesis is a multi-factorial and multistage process from basal cell hyperplasia to dysplasia, to carcinoma *in situ*, and eventually to invasive carcinoma, which is accompanied by alterations of critical growth-regulatory genes in each histologically detectable progression. Many forms of genetic variations, such as single nucleotide polymorphisms, chromosomal insertions, deletions, duplications, and microsatellite instability have been reported to be associated with the risks and prognosis of ESCC. Regarding the genetic polymorphisms for ESCC, genes involved in the metabolism pathway of carcinogens, DNA repair, cell cycle and apoptosis have generally been studied with great interest. These include families of cytochrome p450, glutathione S-transferase, microsomal epoxide hydrolase, ADH and ALDH enzymes.[66] Fagundes et al reported that p53 protein was expressed in a stepwise fashion from normal mucosa to dysplasia, and to carcinoma.[49] Focusing on Lugol unstained areas, Kaneko et al suggested that p53 mutations were detected more frequently in dysplastic samples than non-dysplastic ones.[54] He et al identified loss of heterozygosity in cancerous and precancerous lesions, and the frequency increased with the severity of malignant transformation.[57] Elucidation of these gene–gene and gene–environment interactions may provide novel insights into pathogenesis and strategies to manage ESCC.

Epigenetic markers

Epigenetics are defined as chromatin and DNA modifications without changes in the underlying DNA coding sequence. Ishii et al found that the methylation of CpG islands increased from non-neoplastic epithelium to intraepithelial neoplasia, and to advanced cancer.[55] Roth et al found that the methylation of *p16*, *MGMT*, *RARs2*, *CLDN3*, *CRBP* and *MT1G* tended to increase as histological severity increased.[51] Hibi et al found aberrant p16 promoter methylation in 82% of cancer tissues.[67] Abbaszadegan et al showed that aberrant p16 promoter methylation increased in subjects with a family history of esophageal cancer.[47] Adams et al evaluated the feasibility of use of a panel of four hypermethylated genes in the detection of subjects with high-grade dysplasia.[59] However, the sensitivity and specificity were only 50% and 65%, respectively. Recently, Oka et al found that in mucosa of patients with esophageal cancer, methylation levels of five genes, including *HOXA9*, *MT1M*, *NEFH*, *RSPO4*, and *UCHL1*, were significantly correlated with smoking duration.[68] These epigenetic changes have great potential as novel targets for risk diagnosis and prevention of esophageal cancer.

Early Detection of Esophageal Cancer With Endoscopy

Endoscopy is the gold standard for the diagnosis of esophageal cancer and surveillance of patients with precancerous lesions. Early stage esophageal cancer tends to present with superficial spreading, which is easily overlooked by standard white-light illumination (Figure 1A). Recent advances in image-enhanced endoscopy facilitate the accurate detection of precancerous and superficial cancerous foci (Table 3).[43,44,69–85] Esophageal cancer confined to epithelium and lamina propria have minimal risk of lymph node metastasis and can be cured by endoscopic mucosal resection, submucosal dissection, and radiofrequency ablation, whereas 8% of cancers with muscularis mucosa invasion, and 17–49% of cancers with submucosal invasion, have a risk of lymph node metastasis.[86]

Lugol's chromoendoscopy

Since Lugol's solution can react with glycogen in normal esophageal mucosa but not cancerous lesions, it is widely used to identify superficial

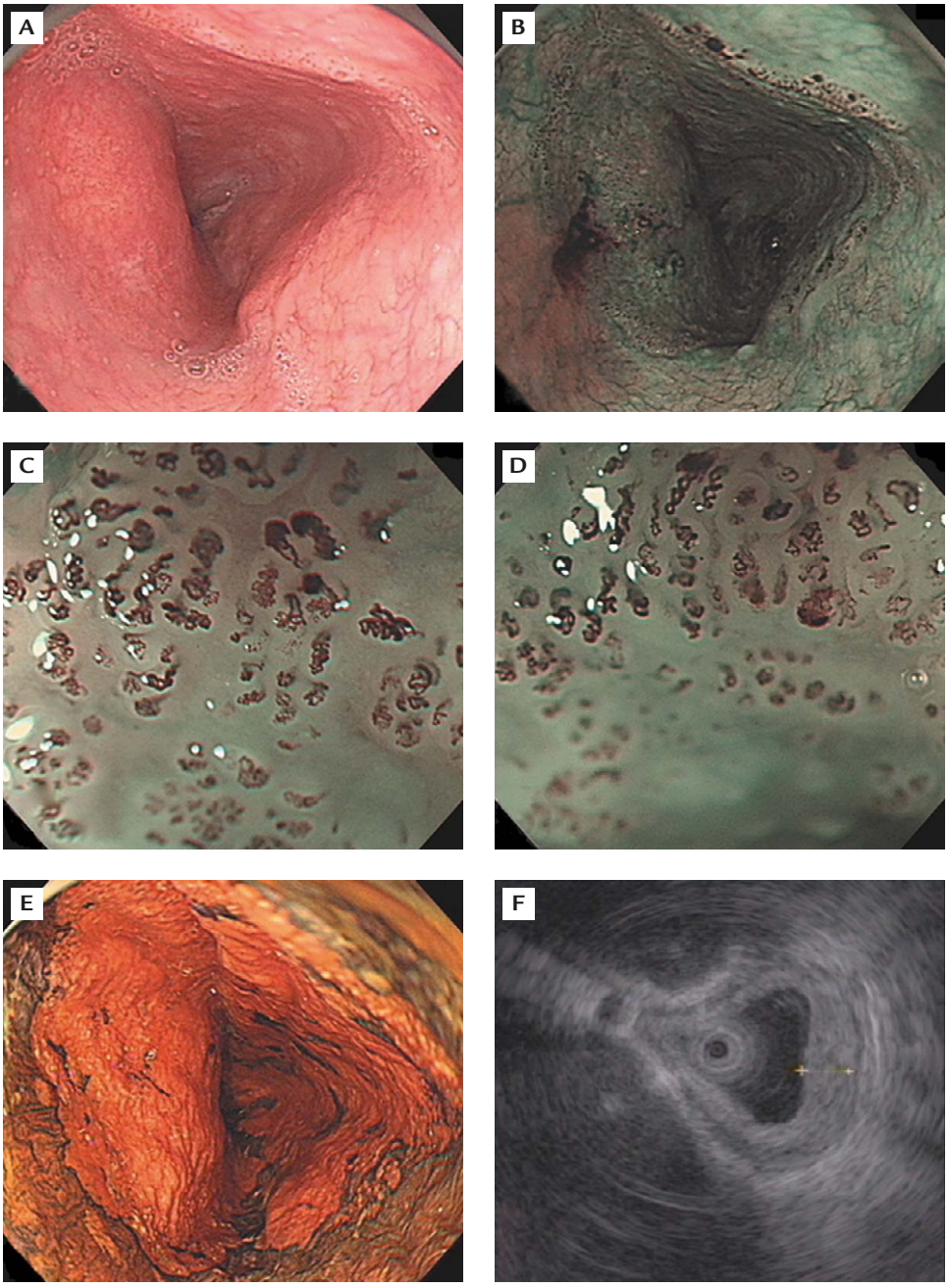

Figure. Endoscopic views of the esophagus. (A) White-light conventional endoscopy shows mildly hyperemic mucosa. (B) Narrow-band imaging endoscopy reveals circumferential brownish discoloration. (C and D) Magnifying endoscopy with a narrow-band imaging system shows intrapapillary capillary loop (IPCL) type V_N. (E) Lugol's chromoendoscopy shows a circumferential Lugol-voiding area. (F) An endoscopic ultrasound discloses thickening of the esophageal wall with involvement of the muscularis propria with T2 invasiveness.

lesions (Figure 1E). Previous studies have shown that Lugol's chromoendoscopy has higher sensitivity and negative predictive values compared with standard endoscopy, however, its specificity and positive predictive value are lower.[70,71,73,74] Shiozaki et al found that 89% of the esophageal cancer disclosed after Lugol staining is at earlier stages and may be cured by minimally invasive treatment.[69] Although Katada et al found that only 17.3% of 434 biopsy specimens from Lugol unstained areas indicated cancerous lesions,[87] the presence of multiple unstained areas over the esophagus was a strong predictor for esophageal cancer (OR = 21.4; 95% CI = 10.63–43.08).[77]

Table 3. Endoscopic detection modalities for the screening of esophageal cancer

Year/location	Patients	Endoscopic modalities	Results	Reference
1990/Japan	178 patients with HNSCC	Lugol staining	ESCC prevalence = 5.1%	Shiozaki et al [69]
1993/Japan	150 patients with HNSCC	Lugol staining	ESCC prevalence = 8.7%	Okumura et al [70]
1995/Japan	629 alcoholic males	Lugol staining	ESCC prevalence = 3.3%	Yokoyama et al [71]
1997/France	158 alcoholics or smokers	Lugol staining	ESCC prevalence = 8.2%	Meyer et al [72]
1998/China	225 patients with dysplasia or cancer	Lugol staining	Sensitivity = 96%; specificity = 63%	Dawsey et al [73]
1999/Brazil	96 high-risk patients	Lugol staining	Sensitivity = 80%; specificity = 63%	Freitag et al [74]
2000/Brazil	60 patients with HNSCC	Lugol staining	ESCC prevalence = 16.6%	Tincani et al [75]
2001/Germany	13 patients with esophageal cancer	AFI	Sensitivity = 97%; specificity = 95%	Mayinger et al [76]
2002/Japan	389 patients with HNSCC	Lugol staining	ESCC prevalence = 14.0%	Muto et al [77]
2004/Japan	41 patients with HNSCC	NBI + magnification	Accuracy of experienced endoscopists: regular magnifying imaging = 81.5%, with NBI = 85.2%	Yoshida et al [78]
2005/Japan	5 patients with superficial ESCC	AFI	Sensitivity = 100%	Uedo et al [79]
2005/Brazil	326 patients with HNSCC	Lugol staining	Prevalence of HGIN and invasive cancer = 7.4%	Hashimoto et al [80]
2006/France	1095 high-risk patients	Lugol staining	ESCC prevalence = 3.2%	Dubuc et al [81]
2006/Germany	87 patients with HNSCC	Lugol staining	ESCC prevalence = 11.5%	Möschler et al [82]
2008/Taiwan	44 patients with HNSCC	NBI + Lugol staining	Prevalence of HGIN and invasive cancer = 25% NBI – sensitivity = 88.9%; specificity = 97.2% Lugol – sensitivity = 88.9%; specificity = 72.2%	Lee et al [83]
2009/Taiwan	27 patients with hypopharyngeal SCC	NBI + Lugol staining	Prevalence of esophageal dysplasia = 14.8% Prevalence of invasive ESCC = 22.2%	Wang et al [43]
2009/Taiwan	36 patients with prior HNSCC	NBI + Lugol staining	ESCC prevalence = 13.9%	Wang et al [44]
2009/Japan	16 superficial ESCC	NBI + AFI + Lugol staining	NBI is better than white light imaging and AFI but cannot replace Lugol staining	Yoshida et al [84]
2009/Taiwan	50 patients with HNSCC	NBI + magnification	ESCC prevalence = 28.0%	Lee et al [85]

HNSCC = Head and neck squamous cell carcinoma; ESCC = esophageal squamous cell carcinoma; AFI = autofluorescence imaging; NBI = narrow band imaging; HGIN = high-grade intraepithelial neoplasia.

Narrow-band imaging and magnifying endoscopy

Narrow-band imaging (NBI) can enhance visualization of microvascular structures in superficial mucosal layers,[88] with the neoplastic lesion under NBI appearing brownish (Figures 1A and 1B). The size of the intrapapillary capillary loop in normal esophageal mucosa is about 10 μm, which will change during tumor angiogenesis. Magnifying endoscopy with NBI can visualize these intrapapillary capillary loop patterns, enable differential diagnosis between cancerous or noncancerous lesions, and predict the invasiveness of cancerous lesions (Figure 1C and 1D).[78,88] The feasibility of NBI with a transnasal ultra-slim endoscope has been confirmed for head and neck cancer patients with tumor-related airway compromise or post-irradiation trismus.[43,44,83] In comparison with Lugol chromoendoscopy, NBI can especially minimize the risk of obtaining false-positive results, especially in patients with multiple Lugol unstained areas.[83]

Autofluorescence imaging

Autofluorescence imaging (AFI) systems produce real-time pseudo-color from the computation of detecting natural tissue fluorescence from endogenous fluorophores.[76,79] Mayinger et al used this system to successfully detect patients with esophageal cancer.[76] Uedo et al also found that AFI can identify flat or isochromatic lesions, which could easily be missed by conventional imaging.[79] However, false-positive interpretations may happen frequently in cases with benign ulceration or non-specific inflammation.

Multiple Modality Approach in Endoscopic Screening

The intention of image-enhanced endoscopy technologies is to increase the detection rate of small precancerous and cancerous lesions. However, since a perfect diagnostic tool is still lacking, several efforts have evaluated the feasibility of multiple detection modalities in a single endoscopic session, in which each modality may offer complementary information that can minimize the risk of obtaining false-negative results. For instance, using NBI before spraying Lugol's solution can overcome the problem of the high false-positive rate of Lugol chromoendoscopy.[83] Advanced endoscopic technology has incorporated high-definition white-light imaging, NBI, and AFI into one system, namely the tri-modal system. A recent study has confirmed its usefulness in screening for early cancerous lesions for patients with Barrett's esophagus.[89] Further studies are needed to evaluate the efficacy of this approach in the screening of esophageal cancer.

The Cost-effectiveness Issue

Cost-effectiveness is a significant concern at present. Lessons from Western countries showed that screening and surveillance for Barrett's esophagus has an annual risk of 0.5–1.0% of becoming esophageal adenocarcinoma.[90,91] There was no randomized trial evidence to support the robustness of models and the variation in parameter selection between studies was large. In our population, by contrast, the progression from precursor lesions to invasive squamous cell carcinoma is accelerated, simultaneous development of multiple cancers is common, and the cost of endoscopic screening is oppositely low. All of these observations may support that screening and surveillance are more likely to be cost-effective for ESCC. However, our current evidence to support this assumption is very limited and requires further economic evaluation alongside cancer prevention trials.

Conclusion

Although the avoidance of smoking, alcohol, and betel quid chewing could reasonably decrease the risk of esophageal cancer, the rigid control of these substances remains unsuccessful. Accordingly, studies have focused on better methods to identify

high-risk subjects and to improve the detectability of small cancerous foci with endoscopy, i.e. a two-staged approach. To enable first-stage risk stratification, further validation of demographic and molecular markers is warranted. Improvement in modern endoscopic technology has strongly enhanced our ability, in the second stage, to confirm the diagnosis. Minimally invasive treatments, such as local endoscopic resection, argon plasma coagulation, and radiofrequency ablation, are therefore possible. These techniques may preserve swallowing, maintain quality of life, and provide meaningful improvement with regards to long-term prognosis.

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