



Status of diagnosis and treatment of esophageal cancer and non-coding RNA correlation research: a narrative review

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Objective: To describe and discuss the progression of the non-coding RNA as biomarkers in early esophageal cancer.

Background: Esophageal cancer without obvious symptoms during early stages is one of the most common cancers, the current clinical treatments offer possibilities of a cure, but the survival rates and the prognoses remain poor, it is a serious threat to human life and health. Most patients are usually diagnosed during terminal stages due to low sensitivity of esophageal cancer's early detection techniques. With the development of molecular biology, an increasing number of non-coding RNAs are found to be associated with the occurrence, development, and prognosis of esophageal cancer. Some of these have begun to be used in clinics and laboratories for diagnosis, treatment, and prognosis, with the goal of reducing mortality.

Methods: The information for this paper was collected from a variety of sources, including a search of the keynote's references, a search for texts in college libraries, and discussions with experts in the field of esophageal cancer clinical treatment.

Conclusions: Non-coding RNA does play a regulatory role in the development of esophageal cancer, which can predict the occurrence or prognosis of tumors, and become a new class of tumor markers and therapeutic targets in clinical applications. In this review, we survey the recent developments in the incidence, diagnosis, and treatment of esophageal cancer, especially with new research progresses on non-coding RNA biomarkers in detail, and discuss its potential clinical applications.

Keywords: Esophageal cancer; clinical treatment; diagnosis; non-coding RNA

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Introduction

As one of the most common gastrointestinal tumors, esophageal cancer is a primary malignant tumor that can develop anywhere along the esophagus, originating from the esophageal epithelial cells. With the improvement in human living standards and hence life expectancy, esophageal cancer has shown an alarming upward trend in

both morbidity and mortality and has even become endemic in many parts of the world, especially in developing countries. EC often has two pathologic types: squamous carcinoma (ESCC) and adenocarcinoma (EAC), with mainly common adenocarcinoma in the west, while China is mainly squamous carcinoma. According to the GLOBOCAN2020 database (<http://geo.iarc.fr/today>), 604,100 new cases of esophageal cancer were reported worldwide, accounting

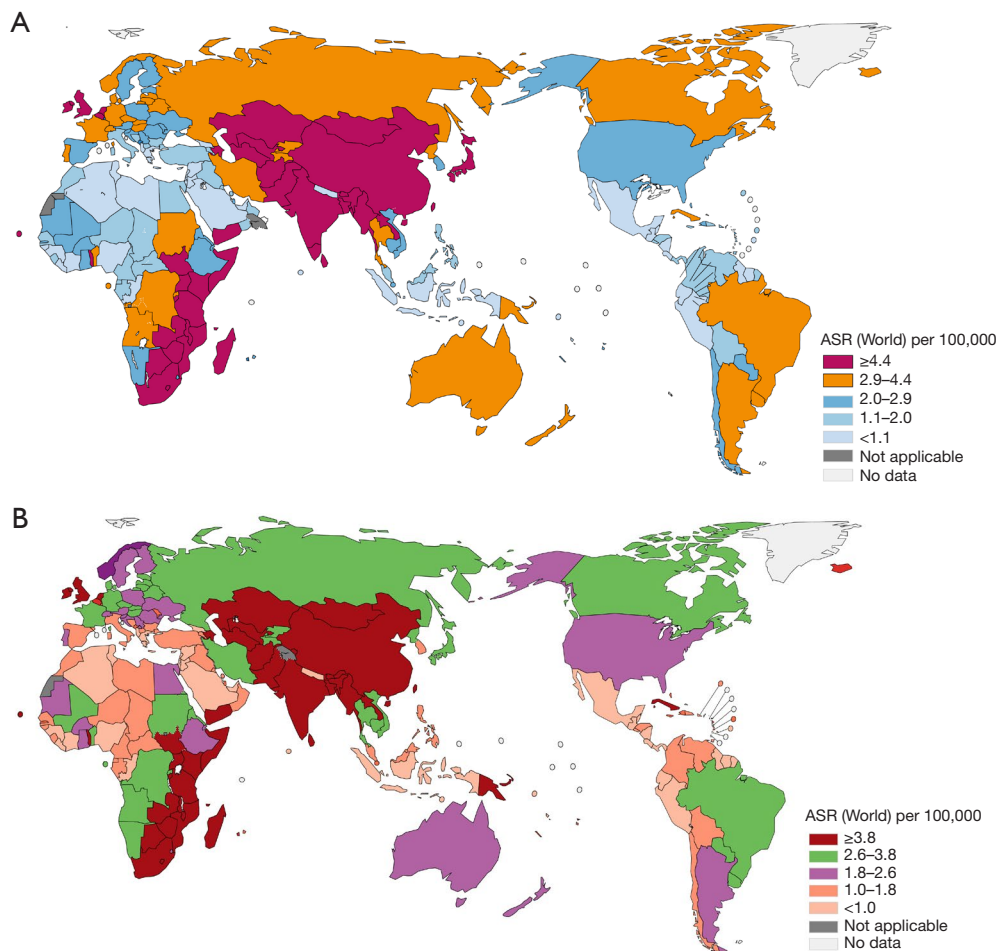


Figure 1 Age-standardized incidence and mortality rates (world) in 2020. (A) Age-standardized incidence rates (world) in 2020, esophagus, both sexes, all age, ASR (World) per100,000; (B) Age-standardized mortality rates (world) in 2020, esophagus, both sexes, all age, ASR (World) per100,000. Note: all data cite from GLOBOCAN2020 database (<http://gco.iarc.fr/today>).

for 3.1% of all cancer cases and ranking the eighth, and the number of deaths reached 544,076, accounting for 5.5%, ranking the sixth in 2020 alone. Also, the ratio of deaths caused by esophageal cancer to all cancer death cases is 1.7 times that of esophageal cancer cases to all cancer new cases, indicating its poor treatment effect. Esophageal cancer is one of the malignant tumors with the highest incidence variation among all cancers, and the prevalence ratio in high-risk areas is 37 times higher than that in low-risk areas, in China in the year 2020 (Figure 1). The incidence and death rate of oesophageal cancer was 13.8 per 100,000 person-years and 12.7 per 100,000 person-years, and the 5-year prevalence was 24.04 per 100,000. While in Europe, the incidence and death rate is less than in China, 3.3 and 2.7 respectively; The number of new cases of esophageal

cancer reached 324,000, and the global burden rate reached 54 percent; the number of death cases reached 301,000, accounting for half of worldwide, so the highest incidence of esophageal cancer is in China (Figure 2), and researches show that it is highly regionalized, especially high in north China regions, and higher in rural areas than urban areas, forming a typical epidemiological characteristic (1). The morbidity and mortality rates of males are higher than those of females, and the standardized mortality rates of both sexes are higher than the global level in recent years (2).

The sharp increase in the incidence and mortality of esophageal cancer indicates that the prevention, diagnosis, treatment, and prognosis of esophageal cancer are unsatisfactory. Different pathogenic sites lead to a big difference in incidence, therefore the onset of esophageal

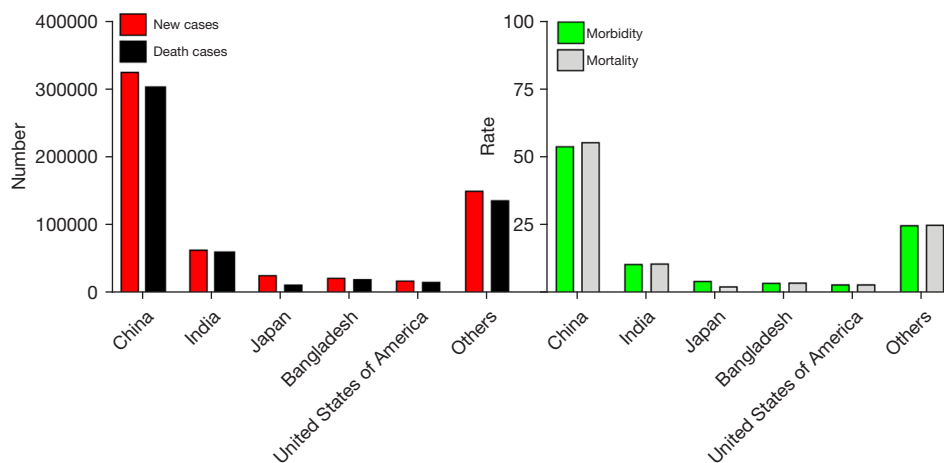


Figure 2 Estimated number of new and death cases of high-incidence countries in 2020, both sexes and all ages. Note: data cite from GLOBOCAN2020 database (IARC website, <http://gco.iarc.fr/today>).

cancer is regarded as a complex process of multi-factor actions, multi-gene controls, and gradual changes (3). Nowadays, it is universally acknowledged that esophageal cancer is related to poor dietary habits, such as eating hot food (4), smoking (5), and ingesting N-nitrosamine compounds (6), which gradually lead to changes in an organism's genetic materials and metabolism, and the cells and tissues grow out of control consequently, resulting in the initiation and progression of esophageal cancer. Recently it also has been reported that esophageal cancer has the possibility of inheritance (7), and the increase of aging population is a main driving factor for the increase in esophageal cancer cases, implying weakened immunity with aging may be the underlying cause of esophageal cancer.

In this review, we begin by discussing the current state of clinical treatment of esophageal cancer, followed by an overview of the recent developments in the incidence, diagnosis, and treatment of esophageal cancer, especially with new research progresses on non-coding RNA biomarkers in detail.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/tcr-21-687>).

Methods

Information used to write this paper was collected by handing searches of the references of retrieved literature, using personal and college libraries to search for texts on keywords, and discussing with experts in the field of clinical

and research of EC (Figure 3). For example, using PubMed and Web of Science, we performed relative articles, searching terms: (((Esophageal cancer) AND (LncRNA)) OR (micro RNA)) OR (circle RNA)) OR (Non-coding RNA). Articles selected were required to be original articles published in English between 2021 and 2011. The article examines studies that contain the latest clinical practices for treating EC in the past 10 years. It should also be noted that the focus of this article is only on research articles, the publication types (*in vitro*, *in vivo* and, *in situ*) is not limited, and news articles, editorials, and unpublished works were excluded.

Clinical treatment

Esophageal cancer is relatively obscure and lacks specific clinical features in its early stage, therefore when most patients suffer from the symptoms of gradual dysphagia and unconscious weight loss and seek medical help, they are usually in the middle or late stage, missing the best treatment period. At that time, it is harder to get curative treatment, even if they wanted to. And it is of a high probability of recurrences, so they are often advised to choose alternative therapies such as palliative care to control tumor-related clinical symptoms and prolong survival (8-10). As a result, when patients are diagnosed with esophageal cancer, they usually already missed the best chance of cure, which is the fundamental reason for the low overall survival rate and high mortality rate of esophageal cancer patients. Now the treatment strategies for EC are based on TNM-

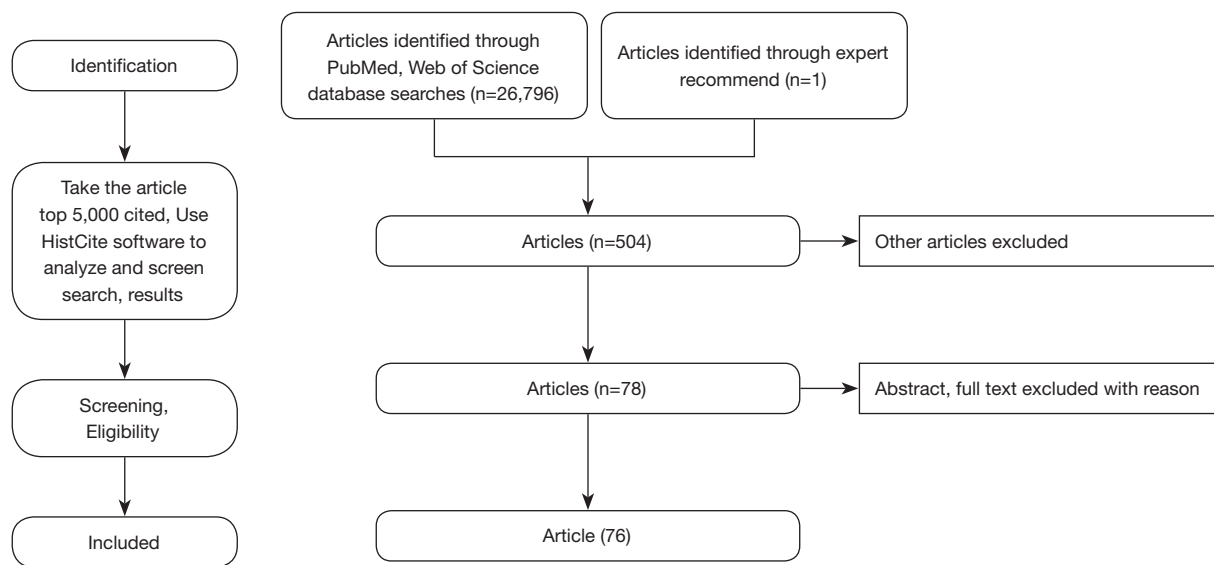


Figure 3 Flowchart of article selection process.

related tumor staging (10).

In the 1960s, Professor Qiong Shen invented the esophageal trawl method and established the diagnosis of esophageal balloon cytology to identify respectable early cancers and precursor lesions, a deflated balloon covered with silk net or cotton is swallowed in the stomach, inflated, and when collected scraping the surface of the esophagus endometrium, smearing on a microscope slide, then fixing the spiders with ethanol, staining with Pap staining, and the cells are read Abnormal signs, which is one of the historic events in the early diagnosis of esophageal cancer (11,12). In the 1980s, endoscopy and iodine staining techniques were widely used in the clinical diagnosis of esophageal cancer, which improved the diagnostic efficiency of early-stage esophageal cancer (13,14). Nowadays, with the continuous development of medical science and technology, more diversified technologies are applied in the early diagnosis of esophageal cancer, such as image logical examinations, pathological examinations, biomarkers, etc. but each has its shortcomings. Imageological examination mainly includes X-ray and CT examination. Studies have shown that CT examination has a higher diagnosis rate than X-rays in the diagnosis of esophageal cancer, avoiding misdiagnosis (15), though, in early-stage esophageal cancer, CT examination cannot detect the situation of the nidus. For the middle or late-stage esophageal cancer, CT examination can not only show the relationship between the nidus and the surrounding structure, reveal enlarged

lymph nodes, but also find the metastasis of distant organs (16). Now imaging diagnosis is usually confirmed by endoscopy and confirmed histopathologically by biopsy, as the “gold standard” for the diagnosis of esophageal cancer. However, the “gold standard” is not 100% accurate due to the requirements of pathological examination on the skill and experience of pathologists and surgeons, and the development of endoscopic technology, especially whether the lesion can be accurately obtained when the lesions are not typical (10). With the rapid development of biomarkers, a new inspection technology emerged (17,18), using the joint detection of tumor markers in the diagnosis of esophageal cancer has high diagnostic efficiency, such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigen 199 (CA-199) and carbohydrate antigen 72-4 (CA72-4). But due to the low specificity and sensitivity of tumor markers, it cannot satisfy the diagnosis needs of all kinds of early esophageal cancers (19,20). It is now found that the diagnosis rate of gastroscopy for middle and terminal stage esophageal cancer is as high as 100% and China has included gastroscopy as one of the routine physical examination items, but the diagnosis rate of gastroscopy for early-stage esophageal cancer is not as precise as that of terminal stage esophageal cancer., The accuracy rate is only about 50% to 60%, thus how to reduce mortality by early-stage esophageal cancer screening is still the focus of future research directions (21).

Currently, the clinical treatments for patients with

Table 1 The Potential algorithm of therapy for extended locally advanced esophageal cancer and salvage treatment

	Early esophageal cancer	Extended esophageal cancer	Locally advanced esophageal cancer	Salvage treatment for local failure of esophageal cancer
Algorithm of therapy	esophagectomy (10)	nimotuzumab combined with chemotherapy (30)	DCF therapy with prophylactic administration of pegfilgrastim (31)	Salvage surgery (32)
	ESD (miR-205 levels may serve as a marker) (33,34)	HiPorfin Photodynamic Therapy (35)	targeted therapy: Gefitinib (36): lapatinib combined with paclitaxel (37)	ER (38)
	EMR (remove lesions only smaller than 2 cm <i>en bloc</i>) (39,40)	combined immunotherapy and chemotherapy (41)	CRT (37)	repeated tPDT (42)

DCF, Docetaxel, cisplatin, and 5-FU; ER, endoscopic resection; CRT, Chemoradiotherapy; tPDT, talaporfin sodium photodynamic therapy; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

middle and terminal esophageal cancer mainly are surgical treatment, radiotherapy, and chemotherapy, among which surgical treatment is the main treatment, and radiotherapy and chemotherapy are adjuvant treatments. In 1913, the first esophagectomy for esophageal cancer was successfully performed in the world, which laid the foundation for surgical treatment of esophageal cancer. Nowadays for early and terminal stage esophageal cancer with distant metastasis, surgery is still the first choice; for stage I and II esophageal cancer, surgical resection is the only possible way to remove the tumor (22,23), but it may have side effects (23,24), such as intraoperative trauma, complication (pulmonary complications and anastomotic fistula, etc. (24), survival problem (such as difficulty in feeding and nutrition, and the long-term survival rate is low) as well as tumor recurrence and metastasis (25). Theoretically, chemo-radiotherapy and other adjuvant therapies can eliminate residual lesion tissues and lesion tissues caused by tumor cell metastasis *in vivo*, thus reducing local recurrence and improving overall survival rate (OS), but there are still problems in radiotherapy sensitivity and resistance to chemotherapy drugs (26). Along with the continuous renewal of medical pieces of equipment and the improvement of medical technology, minimally invasive surgery (27), photodynamic therapy (28), thoracoscope technology (29) are also applied in the treatment of esophageal cancer, but still exist problems, such as low survival rate and high recurrence rate. Because esophageal cancer is relatively obscure and lacks specific clinical features in its early stage, most patients who experience gradual dysphagia and unconscious weight loss seek medical help when they are usually in the middle or late stages, missing out on the best treatment options. At

that time, it is harder to get curative treatment, even if they wanted to. In addition, because there is a high probability of recurrence, patients are often advised to choose alternative therapies such as palliative care to control tumor-related clinical symptoms and prolong survival (8-10). As a result, when patients are diagnosed with esophageal cancer, they usually already missed the best chance of cure, which is the fundamental reason for the low overall survival rate and high mortality rate of esophageal cancer patients.

The current clinical treatment for patients with effect is not ideal enough, it still needs further development and progress (Table 1).

Previous studies on the genomics of esophageal cancer

Cancer is the disease with the highest mortality rate. It originates from the disorder of related genes. The main mechanisms include insertion of enhancers or promoters, reduction of GTPase activity, structural mutations or deletions of key genes, etc. (43-49). However, this may not necessarily cause malignant transformation of cells during part of the tumor formation process. It must be caused by the combination of genes or other factors that affect cell proliferation and apoptosis (48,50). Esophageal cancer-related studies have proved that esophageal cancer is a complex disease. Its occurrence, development, metastasis, and other processes are caused by multifactorial abnormalities such as carcinogen metabolism activation and inactivation, cell proliferation, and apoptosis, and are accompanied by damage repair Multi-gene mutations such as related genes and regulatory genes provide a strategy for

studying the genetics and epigenetics of different cancers (51-53). In the past semi century, researchers worldwide on the pathogenesis of esophageal cancer have made a series of achievements in genes, protein, and metabolic levels (54), but the exact pathogenesis of esophageal cancer is still unknown and still under active research and exploration. At the genomics level, the International Tumor Genome Collaboration Consortium (ICGC) was formally established and launched a global cancer genome research work in 2007, which conducts tumor molecular-level researches from the variation of DNA sequences and maps somatic gene mutation profiles. Till now, many research teams from different countries have summarized data on specific cancers and reported their research results including esophageal cancer. There are researches on the gene-level systematic analysis of esophageal cancer, such as genetic alterations, over-expression of molecules thought to cause malignant transformation, related single nucleotide variations (SNP) and other genetic variations, and exploring driver genes and corresponding signal regulatory networks, Genomics studies of esophageal cancer have found that gene expression disorders are expected to serve as a marker for early diagnosis of esophageal cancer (55,56), and DNA methylation may also indicate the occurrence of tumors, such as EPB41L3 (57), STK3 (58) promoter AKAP12 (59) and so on, which have been proved to be used as a biomarker for the early diagnosis of esophageal cancer.

Non-coding RNA and esophageal cancer

After the completion of the Human Genome Sequencing Project, it is confirmed that only about 2% of the genes in the entire transcriptome can be transcribed and translated into proteins, more than 90% of the remaining cannot be used to encode proteins but can be transcribed into RNAs. However, then the ENCODE research project has discovered that 75% of the genome sequence could be transcribed into RNA, among which nearly 74% of the transcripts are non-coding RNAs (ncRNA, non-coding RNA). In follow-up researches, non-coding RNAs have been gradually confirmed to play a pivotal role in the life activities of humans and many other species, regulating different levels of gene expression (60-62). Till now, the types of non-coding RNAs with regulatory effects mainly include long non-coding RNA (lncRNA), microRNA (miRNA) (63), and novel endogenous non-coding RNA - circular RNA (circRNA) (64).

There conclude some methods for the detection and

verification of non-coding RNA biomarkers for early diagnosis of esophageal cancer (*Figure 4*) (65-71) such as genome-wide profiling, RNA-seq. After rigorous sequencing technology, the differential expression between the groups is compared, and then the bioinformatics correlation analysis is performed to obtain the effective and desired target RNA, and the experimental verification and value evaluation at different levels are carried out. RNA-seq and microarray are the two popular methods employed for genome-wide transcript profiling. Among the several methods, RNA-seq and microarray stand out as the two widely used genome-wide gene expression quantification methods (72-75), RNA-Seq is the direct sequencing of transcripts by high-throughput sequencing technologies, microarray is using the principle of molecular hybridization, the compared specimen (labeled) is hybridized with the microarray, and the intensity of the hybridization signal and data processing are detected to convert it into a specific gene abundance so that the difference in gene expression level of the different specimens is comprehensively compared, they have their own advantages and disadvantages (*Table 2*) (76-83). Leveraging RNA-seq for daily diagnostic activities is no longer a dream but a consolidated reality, it is a powerful technology that is predicted to replace microarrays for transcriptome profiling (84), although established best practices exist. Managing RNA-seq data is not easy, such as plan library preparation, budget optimization, accuracy of downstream sequencing, data assembly, and comparison, *etc.* it still faces many challenges (85-87).

With the development of high-throughput sequencing technology, researches on non-coding RNAs of esophageal cancer have been deepened, and researchers have found several biomarkers for the diagnosis, therapeutic effect evaluation, and prognosis judgment of esophageal cancer.

LncRNA and esophageal cancer

LncRNA is a class of non-coding RNA that regulates gene expression with a length of more than 200 nucleotides and is characterized by its huge amount, various action patterns, conservation in evolution, and several broad categories, including sense, antisense, bidirectional, intronic, and intergenic, all of which have a certain association with cancer (88,89). Researches of recent years have found that lncRNAs not only participates in a variety of biological activities of gene level, chromosome level, and material transportation aspect but also play a more extensive, elaborate, and complex regulatory role than microRNAs

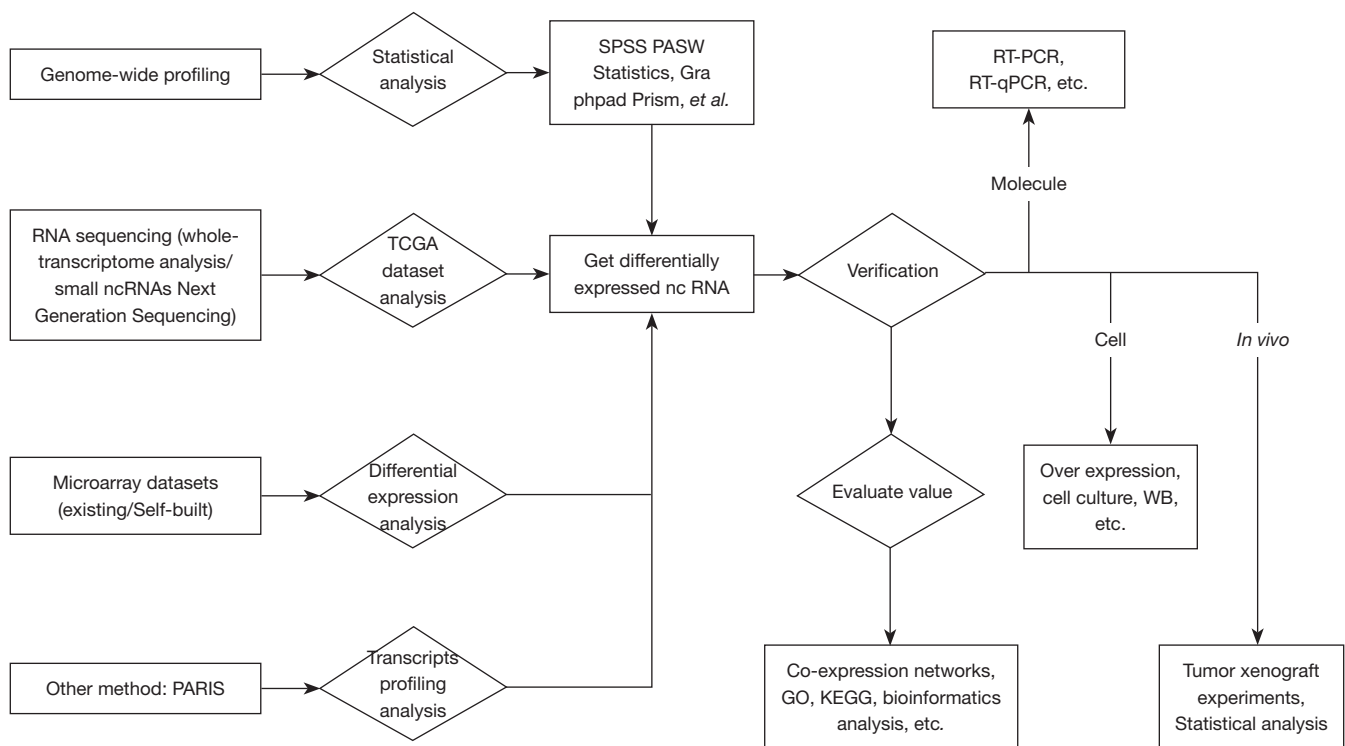


Figure 4 Common methods for the detection of non-coding RNA biomarkers.

Table 2 Comparison of the advantages and disadvantages of RNA-seq and microarray

	RNA-seq	Microarray
Afford	Company	Laboratory, company
Technology limitation	Short sequence reads, not map uniquely to a single gene or isoform (mapping uncertainty),	Background hybridization, cross-hybridization, specific hybridization, probe design
Testing dynamic range	Wider (low to extremely abundant, more sensitive, accurate)	Cannot distinguish “no” from “low” expression.
Data analysis	Far from mature, vulnerable to general biases and errors, the absence of a gold standard for analysis	Relatively simple, faster
Cost	Expensive	Cheap
Advantage	Can discover unknown transcripts and rare transcripts, higher detection throughput, highly reproducible, with relatively little technical variation	Can provide highly consistent data, the analysis software is quite mature, and give clinical diagnostic value

in cell differentiation and development, gene expression, heredity and so on (90-93). Various lncRNAs have been proved to promote or inhibit tumor formation and transfer (94,95). Also, a variety of researches confirmed that many lncRNAs in esophageal cancer are differentially expressed and performing important regulation functions (96-99). These differentially expressed lncRNAs have been

studied to further reveal their biological functions and molecular mechanisms, and have shown their potential to be biomarkers of esophageal cancer or potential therapeutic targets for esophageal cancer (Table 3): Using the method of real-time fluorescent quantitative PCR (RT-qPCR), it was found that LINC00152 is highly expressed in esophageal cancer, and LINC00152/EZH2/

Table 3 List of common lncRNA biomarkers for esophageal cancer

Name	Expression	Mechanism	Biomarker potency	Site of detection	Detection method	Reference
LINC00152	↑ (100)	Interacts with EZH2, positively regulate the expression of ZEB1, enhance the EMT of EC cells (101)	(i), (iii)	Whole blood (100), Animal (100,101) (a, b)	RT-qPCR, Tumor formation study,	(100,101)
HOTTIP	↑	Up-regulated snail1 by competitively binding miR-30b, regulate the Hottip-miR-30b-HOXA13 axis in ESCC	(i), (ii), (iii)	Tumor, cell line (a)	RT-qPCR, Dual-luciferase reporter assay	(102)
FOXD2-AS1	↑ (103)	Regulate miR-145-5p/CDK6 axis, significantly inhibit the proliferation and invasion of esophageal cancer cells (104)	(i), (iii), (iv) (103,104)	Tumor (a)	RT-qPCR, WB	(103,104)
HOTAIR	↑ (97)	HOTAIR decreased WIF-1 expression, regulate HOTAIR/WIF-1 axis (105)	(ii) (106,107)	Tumor, serum (a)	Microarray, RT-qPCR	(97,105-107)
PVT1	↑	Competitively bind miRNA- 203, regulate the expression of human recombinant LIM and SH3 protein 1 in ESCC	(ii)	tumor, mice (a, b)	RT-qPCR, Immunohistochemical, Tumor formation study,	(108)
AK001796	↑	Regulate the MDM2/P53 signal pathway in ESCC	(ii)	Tumor, mice (a, b)	RT-qPCR, RT-PCR, Tumor formation study,	(109)
MEG3	↓	Interact with MI R-4261, inhabit recombinant DKK2 and block Wnt/ β -catenin signaling, inhibit the occurrence and development of ESCC	(i), (ii)	Tumor, mice (a, b)	RT-qPCR, Luciferase reporter assay, WB, Tumor formation study,	(110)
LncRNA-TUSC7	↓	bound to miR-224, miR-224 specifically bound to DESC1, DESC1 inhibited chemotherapy resistance of ESCC cells via EGFR/AKT	(i), (iii), (iv)	Tumor (a)	RT-qPCR, bioinformatics	(111)

↑, represents up-regulated gene expression in tumor tissue; ↓, represents down-regulated gene expression in tumor tissue; (i), diagnostic; (ii), prognostic; (iii), therapeutic; (iv), metastasis monitoring. RT-qPCR, real-time quantitative PCR; WB, western blot; RT-PCR, reverse transcription PCR; ESCC, esophageal squamous cell cancer.

ZEB1 axis could regulate the Epithelial-to-mesenchymal transition (EMT) of esophageal cancer cells and resistance of EC cells to oxaliplatin (L-OHP), thus could present a potential diagnostic marker and therapeutic target for the treatment of esophageal cancer (100,101). Another lncRNA HOTTIP, which was first discovered in a case of gastric cancer, recently has been found to be expressed significantly higher in esophageal cancer areas than in normal tissues, which upregulated snail1 by competitively binding miR-30b and subsequently promoted epithelial-mesenchymal transformation (EMT). In addition, the overall survival rate of esophageal cancer patients with high expression of lncRNA HOTTIP is significantly lower than that with low expression, thus Hottip-miR-30b-HOXA13 axis may be a potential diagnostic marker

or drug target for ESCC therapy and HOTTIP could be used as a molecular marker for the prognosis of esophageal cancer patients (102). Another highly expressed lncRNA FOXD2-AS1 participates in the regulation of miR-145-5p/CDK6 axis, and significantly inhibits proliferation and invasion of esophageal cancer, thus has functions of clinically determining markers and therapeutic targets for lymph node metastasis (103,104). LncRNA HOTAIR, first discovered in breast cancer and highly expressed in esophageal squamous cell carcinoma, has the ability to inhibit tumor cell apoptosis and promote tumor metastasis because it finds that HOTAIR directly decreased WIF-1 expression by promoting its histone H3K27 methylation in the promoter region and then activated the Wnt / β -catenin signaling pathway, and now HOTAIR has been reported

as an indicator of survival and a prognostic tumor marker for patients (97,105-107). PVT1, whose expression is significantly higher in esophageal squamous cell carcinoma tissues than in paracancerous tissues, promotes tumor progression by competitively binding with miRNA-203 to regulate the expression of human recombinant LIM and SH3 protein1 (LASP1) and is often used in clinical practice to predict the overall prognosis of ESCC patients (108). LncNAAK001796, which regulates the MDM2/p53 signaling pathway, not only is highly expressed in esophageal squamous cell carcinoma but also could inhibit cell cycle and tumor growth after being knocked out, therefore can be used as an adverse prognostic factor to determine the prognostic quality (109). MEG3, lowly expressed in esophageal cancer, shown in studies that its mechanism of action is as a sponge of miRNA-4261 to inhibit recombinant human Dickkopf-related protein 2 (DKK2) thus block the Wnt/ β -catenin (β -catenin) signaling pathway (110), has its role of predicting tumor progression and as a prognostic marker, LncRNA-TUSC7, significantly down-regulated in ESCC tissues and could significantly inhibit the migration, chemotherapy resistance and invasion ability of esophageal cancer cells through the expression of related proteins, can be used as a molecular marker for the diagnosis and treatment of esophageal squamous cell carcinoma and metastasis monitoring (111). In addition to the above signaling pathways, the involvement of lncRNAs has also been found in EGFR/SATA1, RAS/MARK pathways, and so on (112). Among them, the highly expressed LINC00152 discovered in the study was collected from 76 patients with disease tissues, and RT-PCR was used to prove that its expression was also up-regulated. Then, through related experiments on cell lines and mouse models, the molecular marker function was further confirmed, so it is speculated that it is possible to further advance clinical research. Therefore, the role of lncRNA in esophageal cancer is incomparable, and it is of great importance to study it.

MicroRNA and esophageal cancer

In recent years, cancer has become one of the most serious threats to human life and health, and miRNAs play an important role in cancer. It was first confirmed by Calin *et al.* in 2004 using human precursor cells and the microarray of mature miRNA oligonucleotides probes, reporting the genome-wide expression profile of miRNA in human B-cell chronic lymphocytic leukemia (CLL) and confirming that the differential expression of genes is related to Zap-70,

and these data indicate that miRNA expression patterns will affect leukemia biology and clinical behavior (113). Since then, along with the rapid development of molecular biology, studies on the relationship between miRNAs and tumors have gradually become clearer, and more miRNAs have been proved to play an important role in the forming of tumors. Due to these studies, the biological functions of the miRNAs have gradually become clearer. Multiple data have proved that some specific miRNA expression will get increased or decreased between the tissues getting cervical cancer (114), prostate cancer (115), gastric cancer (116), esophageal cancer (117), adjacent tissues, and abnormal expression also occurs when genetic or epigenetic changes occur (118). After in-depth research on the relationship between miRNA and tumors, it is found that these miRNAs have different functions, which can be divided into two categories: miRNAs up-regulated in tumor cells and miRNAs down-regulated in tumor cells. MicroRNAs highly expressed in tumor tissues stimulate the over-expression of oncogenes while those whose expression is down-regulated are reduced or even silenced in tumor cells (119), thereby affecting the occurrence, development, invasion, and metastasis of cancer. Some scholars even found that the expression level of some miRNAs also affects the overall survival rate of patients with esophageal cancer when studying the relationship between esophageal cancer and miRNA (120-122), such as miRNA221 (123), miRNA23a (124), miRNA193-3p (125), etc. This also shows that miRNAs can be used to assess the overall survival of the esophageal cancer patients. Compared with the traditional tumor markers, with low specificity and weak sensitivity, miRNAs are evolutionarily conserved in the human body, widely distributed in easily accessible body fluids, and have high stability. Therefore, miRNAs are a new type of diagnostic marker with great potential. As diagnostic markers, miRNAs are also used in various aspects of clinical treatments of esophageal cancer (*Table 4*): For example, the most classic small-molecule RNA miRNA21 used in the treatment of various tumors has also been found with higher expression in esophageal cancer tissues than normal tissues. It has been experimentally verified that miRNA-21 in esophageal cancer will target the key protein of the PTEN /PI3K/AKT signaling pathway, therefore, affects the proliferation and apoptosis of tumor cells and other life activities, thus miRNA-21 can be used at the diagnosis, treatment, and prognosis of esophageal cancer (126-128); Highly expressed miRNA miR-18a, similar to miR-21, regulates the PTEN-PI3K-AKT-mTOR signal

Table 4 List of common miRNA biomarkers for esophageal cancer

Name	Expression	Mechanism	Biomarker potency	Study setting	Detection method	Reference
miR-21	↑ (126,127)	Target the key proteins of the PTEN/PI3K/AKT signal pathway (128)	(i), (ii), (iii) (126-128)	Serum (126), tumor (127,128) (a)	RT-qPCR (128), Affymetrix GeneChip miRNA 1.0 Array (127)	(126-128)
miR-18a	↑ (129)	Regulate the PTEN-PI3K-AKT-mTOR signal axis, increase the expression of cyclin D1 in ESCC (130)	(i), (ii) (collaborate with miR-21 will get higher sensitivity and better effect) (129,131)	Serum (129), tumor (129-131) (a, b)	RT-PCR (129), RT-qPCR (130,131), IHC (131), WB (131), Tumor formation study	(129-131)
miR-17/20a	↑	Inhibit Tβ-β / integrin β6 subunit pathway by targeting TβR2 and Smad anchor receptor activation and degradation in ESCC	(i), (ii)	cell lines, mice (a, b)	qPCR, IHC, Tumor formation study,	(132)
mi R-203	↑ (133)	MiR-203 targets MAP3K1, thereby inhibiting cell proliferation and invasion (134)	(ii), (iv) (135)	Tumor (a)	RT-qPCR (133), WB (134), Dual-luciferase reporter assay (134)	(133-135)
miR-1290	↑ (136)	Target NFIX (137)	(iv) (138)	Serum (a)	miRNA microarray	(136-138)
mi R-145	↓ (139)	Target SMAD5, promote cell proliferation and migration/ invasion (140)	(ii), (iii) (141)	Tumor, cell, mice (a, b)	RT-qPCR, WB, IHC, Luciferase reporter assay	(139-141)
miR-143	↓ (142)	MAPK7 pathway (143)	(iii)	Tumor (a)	RT-qPCR	(142,143)
miR-122	↓	Target and down-regulate PKM2 to inhibit the proliferation of esophageal carcinoma cells	(iii)	Cell (a)	Bioinformatics analysis, RT-qPCR, WB	(144)
miR-133b	↓ (145)	Down-regulate the expression of EGFR in ESCC to inhibit MAPK/ ERK and PI3K/AKT pathway (146)	(i), (ii)	Tumor, cell, mice (a, b)	RT-qPCR (145), WB (146), Tumor formation study,	(145,146)

↑, represents up-regulated gene expression in tumor tissue; ↓, represents down-regulated gene expression in tumor tissue; (i), diagnostic; (ii), prognostic; (iii), therapeutic; (iv), metastasis monitoring. RT-qPCR, real-time quantitative PCR; WB, western blot; RT-PCR, reverse transcription PCR; ESCC, esophageal squamous cell cancer.

axis, increases the expression of cyclin D1 and promotes the proliferation of esophageal squamous cell carcinoma cells, and shown in studies that it can be used not only as a prognostic indicator of esophageal cancer but also as a diagnostic biomarker (collaborate with miR-21), will get higher sensitivity and better effect (129-131); Jing *et al.* by getting microRNA chip via RT-q PCR assay demonstrated that miR-17/20a overexpression can inhibit Tβ-β / integrin β6 subunit pathway by targeting TβR2 and Smad anchor receptor activation and degradation. Therefore, miR-17/20a can be used as diagnostic and prognostic markers (132). MAP3K1 was a direct target of miR-203, which was first

discovered in breast cancer and whose expression level is much higher in esophageal cancer tissues than in adjacent tissues. Overexpression of MAP3K1 can eliminate the inhibition of miR-203 on cell proliferation and invasion, MiR-203 is clinically used to determine the TNM stage, pathological differentiation, and lymph nodes of esophageal cancer metastasis and is used as a prognostic marker (133-135). MiR-1290, which is highly expressed in esophageal cancer and has been demonstrated to operate as a tumor oncogene in the progression of ESCC by targeting NFIX, has also been used as a prognostic marker (136-138). Except for the fact that up-regulated miRNAs play an

important regulatory role in esophageal cancer, some down-regulated miRNAs, such as the recently discovered miR-145, also play a role in cell proliferation, migration, or invasion, making it a biomarker, treatment target, and prognostic indicator for esophageal cancer (139-141); miR-143 and miR-122, both found differentially expressed in cancer cells and normal tissues, have also been found to be used as therapeutic targets for esophageal cancer (142-144), and miR-133b, with low expression in ESCC, can inhibit the MAPK/ERK and PI3K/AKT pathways (common tumor signaling pathways) by down-regulating the expression of EGFR to resist tumor regulatory role, so can be used for the detection and prognosis of early esophageal cancer (145,146). Using SYBR green real-time quantitative reverse transcription-polymerase chain reaction, the high expression of miR-18a in 105 surgical specimens from ESCC patients was detected, and The miR-18a expression positively correlated with tumor stage, then through further experiments, it was found that comparing traditional esophageal tumor markers, serum miR-18a, and miR-21 are more sensitive to the diagnosis of esophageal cancer, and the combination of traditional esophageal tumor markers can further improve the sensitivity and accuracy of esophageal cancer diagnosis. Therefore, it is speculated that the new miR biomarkers can be combined with each other or even combined with traditional tumor markers to achieve better results.

Although the number of mi RNAs discovered already is not small, the current research on miRNAs is still at a relatively early stage, and the number of experimentally proven microRNAs with clear functions is only a drop in the ocean compared to the number of predicted microRNAs found by bioinformatics methods. Therefore, it is necessary to go deeper in future researches to screen out highly sensitive and specific microRNAs and their corresponding type of esophageal cancer to ensure that more accurate diagnosis and more valuable evaluation results can be provided in future clinical tests.

CircRNA and esophageal cancer

With the continuous development of Next-Generation Sequencing (NGS) technology, low cost, high speed, and high throughput, and the progress of corresponding matching algorithms, the application value of circular RNA (circRNA) in the clinical field of tumors has gradually emerged. Circular RNA, as a type of evolutionarily conservative ancient RNA that has the function of

regulating gene expression in eukaryotic creatures, is a new kind of endogenous non-coding circular RNA (147). It forms a special circular double-stranded closed structure by a covalent bond with variable length and does not have the “cap” and “tail” characteristics of chain RNAs (148,149). Several studies have proved that circRNAs are widely present in a variety of biological cells (150-152). For example, in 1976, circRNA was first discovered in a viroid in a plant and then was found in animal cells and fungal yeast; so far, tens of thousands of circRNAs have been discovered, and they can be divided into three types according to their constituent sequences and sources: circular intronic RNA (ciRNA) (153) and exonic circRNA (ecircRNA) (154) and exon-intron circRNA (ElciRNA) (155). And these three types of circular RNA molecules are universally acknowledged to be formed by two kinds of synthetic mechanisms: direct reverse splicing and lasso-driven cyclization (156,157). CircRNA is a kind of particular RNA molecule with special structures, which is not comparatively easy to be recognized and degraded by enzymes, and it is not completely dependent on the linear mRNA expression of parent genes. CircRNA is specifically expressed and plays an important role in cells, tissues, and ontogenetic stages, with strong stability and Spatio-temporal specificity (148,158,159). After the in-depth study of circular RNAs, it has been found that circRNAs are mainly involved in the regulation of biological processes at the transcriptional and post-transcriptional levels, and nowadays its universally acknowledged that the main mechanisms of circRNAs are involved in alternative splicing, the transcription process, adjusting the parent gene expression, acting as microRNA molecular “sponge”, regulating RNA-binding protein, participating in protein translation and so on (97,160-164), among which, molecular sponge action is the most classic mechanism of circRNAs. Molecular sponge action refers to the biological regulation process of miRNA inhibition and up-regulation of target gene expression when a circRNA has a specific site that could bind to a miRNA. Till now the mechanism has also been proved by a large number of experiments (154,165,166).

With the in-depth research on the structure, mechanism, and function of circRNAs, it has been found that circRNAs not only play an important biological function in physiological processes but also plays a crucial role in the occurrence and development of diseases, such as viral hepatitis (167), vascular diseases (168), central nervous system degenerative diseases (169,170), diabetes (171),

Table 5 List of common circRNA biomarkers for esophageal cancer

Name	Expression	Mechanism	Biomarker potency	Study setting	Detection method	Reference
ciRS-7	↑ (175)	As miR-876-5p and miR-7 sponge, inhibit them to regulate antigen MAGE-A family in ESCC (175,176)	(i), (iii) (175)	Tumor (a)	RT-PCR	(175,176)
CircHIPK3	↑	Regulate P53-Akt-Mdm2 signal pathway in ESCC	(iii)	Tumor (a)	RT-qPCR, Bioinformatics analysis, WB	(177,178)
circ-0006168	↑	Target regulate miR-100/mTOR and miR-339-5p/CDC25A pathway	(i), (iii)	Tumor, cell (a)	RT-qPCR, Dual-Luciferase reporter system	(179)
hsa_circ0004771	↑	Regulate miR-339-5p/CDC25A pathway in ESCC	(i), (ii) (low invasive biomarker)	plasma (a)	RT-qPCR	(180)
circVRK1	↓	Regulate miR-624-3p/PTEN/PI3K/AKT signaling pathway	(iii)	Tumor, cell (a)	RT-qPCR	(181)
circ-ITCH	↓	Make miR-7, miR-17, miR-214 molecular sponges, enhancing the expression of ITCH to ubiquitin degrade phosphorylated DVL2 and thus inhibit the development of the Wnt pathway in ESCC	(iv)	Tumor, cell, mice (a, b)	RT-qPCR, Bioinformatics analysis, WB, Tumor formation study	(182,183)
circ-0043898	↓	Participate in the synthesis of tumor proteoglycan and RAP1 and mTOR signaling pathways	(i), (iii)	Tumor, cell, mice (a, b)	RNA-seq, RT-PCR, GO, KEGG, Tumor formation study	(164,184)

↑, represents up-regulated gene expression in tumor tissue, ↓, represents down-regulated gene expression in tumor tissue, (i) diagnostic, (ii) prognostic and (iii) therapeutic (iv) metastasis monitoring, a in-vitro, b, in-vivo, c, in-situ, RT-qPCR, real-time quantitative PCR, WB, western blot, RT-PCR, reverse transcription PCR, ESCC, esophageal squamous cell cancer.

various cancers (172-174), etc. With the progress of testing technologies and the improvement of medical care, and cancer is gradually found to be the disease with the highest mortality rate, people are paying more and more attention to the diagnose and treatments of cancer. Therefore, as circRNAs have been found in various cancers and have certain regulatory effects, the researches on RNAs in tumors has gradually been focused on the distribution of circRNAs in different kinds of tumors and their roles in tumor genesis and development, especially the molecular mechanism of how circRNAs regulate tumor cells proliferation, apoptosis, invasive movement, and angiogenesis. So far, various studies have identified the abnormal expression of a variety of circRNAs in different tumors, including esophageal cancer (Table 5), which preliminarily reveals the unusual clinical significance of circRNAs. For example, the expression of classical tumor-associated ciRS-7 in esophageal squamous cell carcinoma tumor tissues is significantly higher than

that in normal tissues, in which ciRS-7 is supposed to act as a molecular sponge of miR-7 and miR-876-5p to enhance the antigen MAGE-A family expression. Therefore, ciRs-7 can be used as a potential target for diagnosis and treatment of esophageal cancer (175,176); CircHIPK3, one of the most thoroughly studied circRNA, is up-expressed in esophageal cancer tissues and can be used as a potential therapeutic target for esophageal cancer by regulating P53-Akt-Mdm2 signaling pathway to promote cell proliferation and inhibit apoptosis (177,178). So does circ-0006168, as a potential diagnostic biomarker and therapeutic target, and its mechanism of action is to target and regulate miR-100/mTOR and miR-339-5p/CDC25A pathways to promote the progression of esophageal cancer (179); 20 cancer tissues cases and 105 control cases were detected by RNA sequencing technology and RT-PCR, getting the result that the expression of hsa_circ_0004771 was up-regulated, and the reason why it was of great value for the diagnosis

and prognosis of malignant tumors is that it acted on the miR-339-5p/CDC25A pathway (180). When screening the differentially expressed genes of esophageal cancer patients and normal humans, it was found that there were also down-regulated circRNAs in the esophageal cancer group, which play an important role in the occurrence, development, invasion, and metastasis of esophageal cancer. circVRK1, as potential biomarkers and therapeutic targets for human malignant tumors, and its mechanism of action is that CircVRK1 inactivated PI3K/AKT signaling pathway by up-regulating PTEN and CircVRK1-miR-624-3p-PTEN pathway regulated ESCC progression (181). Circ-ITCH is not only poorly expressed in esophageal cancer, but also compete with the 3'untranslated region (3'UTR) of the messenger RNA of the homologous protein ITCH to bind with the miRNAs related to tumors such as miR-7, miR-17, miR-214, etc., thus reducing the inhibition and enhancing the expression of ITCH, then it plays a regulatory role through ITCH/DVL2/Wnt pathway, so Circ-ITCH is related to cancer formation and could be used to predict tumor progression (182,183); Circ-0043898, discovered in esophageal cancer and significantly down-regulated in esophageal cancer, plays a role by participating in the mechanism of protein synthesis. It has been found that circ-0043898 is involved in the synthesis of tumor proteoglycan, RAPI, and mTOR signaling pathways and has the potential to become a therapeutic target and one of the biomarkers for diagnosis of esophageal cancer (164,184); Also At the same time, high-throughput sequencing technology is commonly used to construct circRNA expression profiles in esophageal squamous cell carcinoma to analyze the differentially expressed circRNA, the highly differentially expressed circRNA obtained seem to be potential biomarkers for esophageal squamous cell carcinoma, such as hsa_circ_0007541, whose expression level in esophageal squamous cell carcinoma tissues significantly differs from adjacent tissues and has a regulatory effect on the progression of the tumor (185). Through the discovery and induction of known biomarkers of esophageal cancer circle RNA, we can see that circle RNA generally regulates cell signaling pathways by acting on miR. This mechanism of action has been obtained in both *in vivo* and *in vitro* experiments. It has been confirmed that, for example, up-regulated ciRS-7 and down-regulated circ-ITCH, their regulation mechanism is to up-regulate or down-regulate the expression of related proteins as the corresponding miR molecular sponges, thereby regulating cell proliferation or decay signaling pathways.

Based on all the above, circular RNAs play an important role in the process of life and could be used as a biomarker for many diseases. However, compared with lncRNAs and miRNAs, the studies of the circular RNAs whose functions are experimentally identified in the researches are still in the preliminary stage. Identifying the specific mechanisms and functions of the circular RNAs is only the tip of an iceberg, it takes a lot of effort to further explore the mysteries of circular RNAs in future researches.

Conclusions

In recent years, with the development of medical technology and the deepening of tumor molecular biology research, tumor markers are helpful to the diagnosis, treatment, and prognosis of patients with esophageal cancer. We found that compared with mRNA, lncRNA and circRNA have higher tissue and Spatio-temporal specificity, and can play a regulatory role at the transcription and post-transcriptional levels in a variety of ways. They are the best candidates for early diagnosis and prognostic biomarkers of the disease. However, the current mechanism of esophageal cancer is not very clear. Some biomarkers are common markers of multiple cancers and have similar abnormal expressions, which are unique to non-esophageal cancer or even early esophageal cancer. Furthermore, many markers are still in experiments. At this stage, although it has been further verified on animal models and has certain reference value, it cannot be fully applied or suitable for human entity disease. It has certain limitations. Therefore, finding effective and specific markers is faced in the diagnosis of esophageal cancer. The main challenge is also an urgent and necessary task. In the future, the best marker profile of non-coding RNA is mainly based on RNA-seq technology, combined with large sample data, to screen and identify RNA molecules specifically expressed in disease tissues or patients, and guide early diagnosis and prognosis of diseases, such as Bioinformatics (186), microarray (187,188) and other methods (189). In addition, different factors such as esophageal cancer pathology, stage of development, age, and other factors can also lead to differential expression of non-coding RNA. Therefore, when developing and evaluating the best marker profile of non-coding RNA, it is necessary to increase the sample size as much as possible and carry out clinical classification. And from the above results, it can be seen that the use of a single marker for early diagnosis of esophageal cancer still has certain limitations. Therefore, in future studies, researchers not only need to pay more

attention to the sensitivity and specificity of tumor markers but also explore the application of the combined detection of multiple markers to ensure the provision of more valuable diagnosis and evaluation results. It is also possible to use a combination of multi-omics techniques to study the mechanism of esophageal cancer occurrence, development, invasion and metastasis, so as to better guide the patients with esophageal cancer diagnosis, treatment, and prognosis!

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