УДК 616.329-018.7-06-006.66
https://doi.org/10.20538/1682-0363-2020-4-226-234

Barrett's esophagus and esophageal adenocarcinoma: biomarkers of proliferation, apoptosis, autophagy and angiogenesis

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ABSRACT

Aim. To analyze all known markers of proliferation, apoptosis, autophagy and angiogenesis in the pathogenesis of Barrett's esophagus and esophageal adenocarcinoma with the purpose of improvement of diagnostics and treatment quality.

Materials and methods. Analysis of the available scientific sources by Russian and foreign authors.

Results. Data on all the known markers has been structured and is supposed to be integrated into clinical practice in the diagnosis and treatment of Barrett's esophagus and esophageal adenocarcinoma at various stages of disease development

Key words: Barrett's esophagus, esophageal adenocarcinoma, proliferation, apoptosis, autophagy, angiogenesis, markers.

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors received no specific funding for this work.

For citation: Petenyova E.S., Salmina A.B., Berdnikov S.I., Salmin V.V., Abramov V.G., Medvedeva N.N., Semichev E.V. Barrett's esophagus and esophageal adenocarcinoma: biomarkers of proliferation, apoptosis, autophagy and angiogenesis. *Bulletin of Siberian Medicine.* 2020; 19 (4): 226–234. https://doi.org/10.20538/1682-0363-2020-4-226-234.

Пищевод Барретта и аденокарцинома пищевода: биомаркеры пролиферации, апоптоза, аутофагии и ангиогенеза (обзор литературы)

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РЕЗЮМЕ

Цель: анализ известных маркеров пролиферации, апоптоза, аутофагии и ангиогенеза в патогенезе пищевода Барретта и аденокарциномы пищевода для улучшения качества диагностики и лечения.

Материалы и методы. Анализ доступной литературы российских и зарубежных авторов.

Заключение. Структурированы данные по известным маркерам, которые в дальнейшем планируется внедрить в клиническую практику при диагностике и лечении пищевода Барретта и аденокарциномы пищевода на разных стадиях развития заболеваний.

Ключевые слова: пищевод Барретта, аденокарцинома пищевода, пролиферация, апоптоз, аутофагия, ангиогенез, маркеры.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования.

Для цитирования: Петенёва Е.С., Салмина А.Б., Бердников С.И., Салмин В.В., Абрамов В.Г., Медведева Н.Н., Семичев Е.В. Пищевод Барретта и аденокарцинома пищевода: биомаркеры пролиферации, апоптоза, аутофагии и ангиогенеза (обзор литературы). *Бюллетень сибирской медицины.* 2020; 19 (4): 226–234. https://doi.org/10.20538/1682-0363-2020-4-226-234.

INTRODUCTION

Barrett's esophagus is a pathological condition in which, under the influence of refluxate (stomach contents: hydrochloric acid, digestive enzymes, bile acids), the non-keratinizing squamous epithelium of the distal esophagus is replaced with specialized columnar epithelium with goblet cells, with the formation of areas with metaplasia and epithelial dysplasia. According to different authors, the frequency of Barrett's esophagus (BE) in the population is 2.4–4% and is a "precancerous disease", therefore, the problem of diagnosis, early detection of BE and monitoring of these patients is extremely important due to the high risk of malignization. In turn, esophageal cancer accounts for 3% and ranks 6th in the structure of all malignant diseases and is the third most common type of tumor of the gastrointestinal tract (after cancer of the stomach and rectum) [1]. The neoplastic progression of BE is expressed by the appearance of areas of metaplasia andan increase in the degree of epithelial dysplasia (low-grade dysplasia – high-grade dysplasia) [2–4]. With the continued effect of refluxate on the esophageal mucosa, in the absence of treatment, esophageal adenocarcinoma (EAC) develops. It is rarely detected in the initial stages of the disease due to the late onset of clinical symptoms which include pain syndrome (which, in clinical practice, is often perceived as a manifestation of other pathological conditions/diseases of the cardiovascular or bronchopulmonary systems), dysphagia, and respiratory issues in the form of a paroxysmal dry cough, and aggravation after eating and in the supine position. In this regard, the possibility of surgical treatment at the time of diagnosis usually does not exceed 50% [4]. The incidence of EAC against the background of BE is steadily increasing, amounting to up to 5% of patients with BE per year, while the five-year survival rate of patients with EAC is extremely low and, according to various sources, is no more than 15% [1, 2, 4]. Predicting malignization, a clear definition of markers will make it possible to track the course of BE, predict the transition to EAC, and, accordingly, facilitate early detection and timely treatment of this pathology.

The search for appropriate markers for the diagnosis of PB is inseparable from the pathogenesis of the disease. The pathogenesis of BE is not well understood. Metaplasia is considered a consequence of the long-term gastroesophageal reflux disease (GERD), in which there is constant contact of aggressive reflux factors with the stratified squamous epithelium of the esophagus.

The main risk factors are male gender, age over 50, clinical symptoms of GERD. Additional factors include Caucasian race, hiatal hernia, obesity (abdom-

inal type), smoking, family medical history and genetic predisposition.

Considering the above, it can be assumed that BE is a stage in the development of EAC. The reasons triggering the development of metaplasia and dysplasia, as well as the molecular mechanisms of the pathogenesis of these conditions, are still poorly understood. There are several theories of the BE development, and discussions continue regarding the mechanisms of the pathogenesis of this pathology.

It is known that in the presence of acid reflux, the flat non-keratinizing epithelium in the damaged mucous membrane of the esophagus is replaced by metaplastic columnar epithelium [2] (Fig. 1–4).

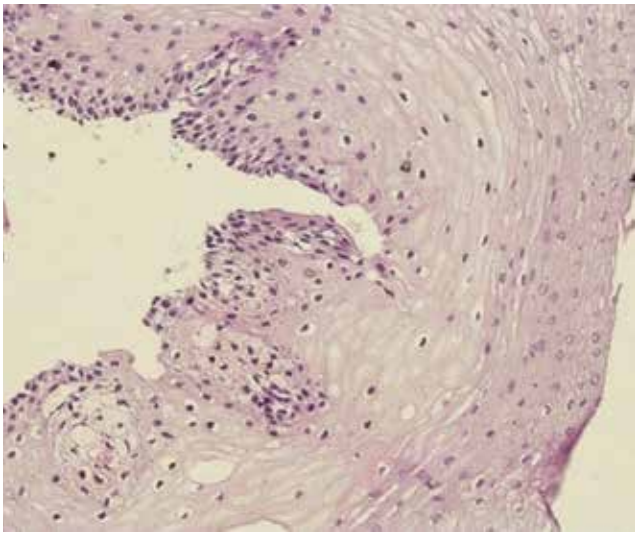

Fig. 1. The esophagus of a healthy person. Stained with hematoxylin and eosin, ×200

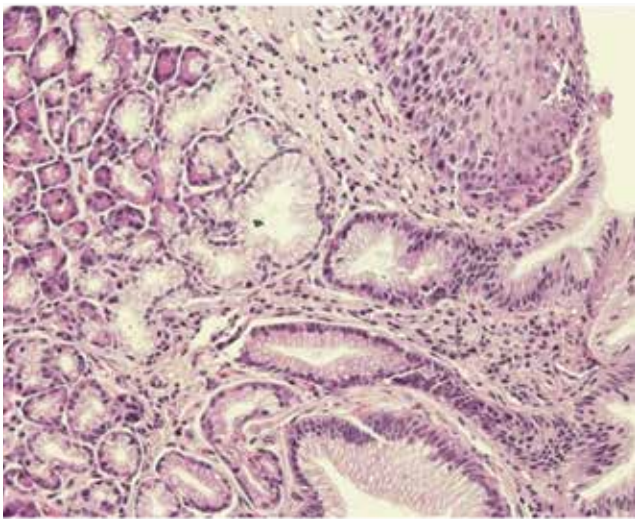

Fig. 2. The area of transition of the esophagus into the stomach in a healthy person. Stained with hematoxylin and eosin, ×200

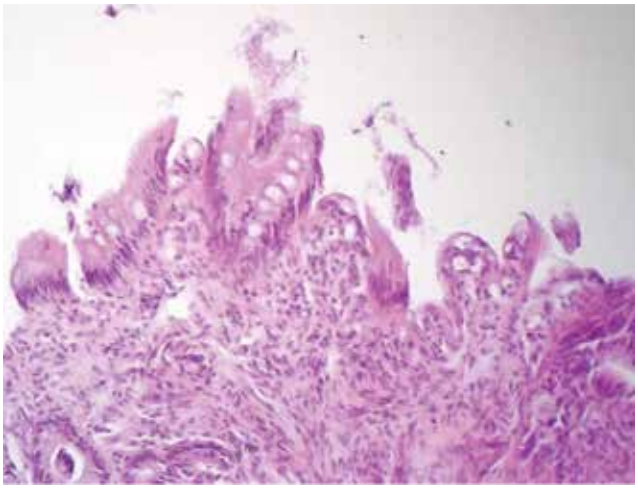

Fig. 3 The mucous membrane of the distal esophagus of a patient diagnosed with BE. Metaplastic type of mucous membrane. Stained with hematoxylin and eosin, ×200

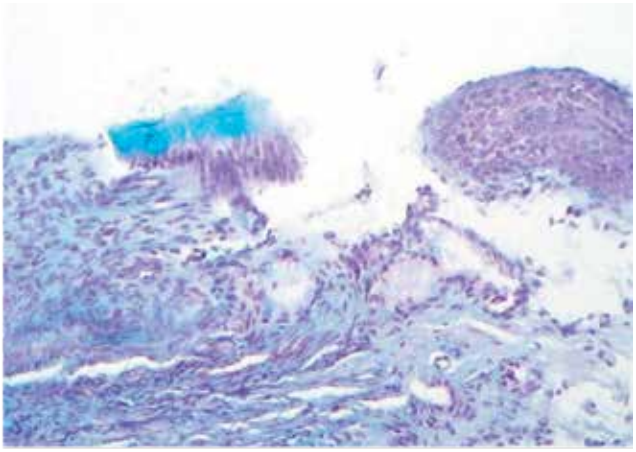

Fig. 4. The mucous membrane of the distal esophagus of a patient diagnosed with BE. Metaplastic type of mucous membrane. Kreiberg mucin staining, ×200

However, daily intraesophageal monitoring of pH and bilirubin revealed that mixed acid-biliary reflux predominates in up to 90% of patients with BE, which causes more severe damage to membranes and intercellular contacts due to the synergistic effect of hydrochloric acid, gastric acid enzymes and bile acid conjugates [4]. Conjugated lipophilic bile acids increase the permeability of apical cell membranes, thereby facilitating the diffusion of hydrogen protons into the tissue, which ultimately has the main damaging effect. Damage to the cells of the surface layer of the epithelium stimulates the regeneration and compensatory thickening of the epithelial layer under the influence of the epidermal growth factor, which leads to an increase in the length of the proliferation zone, the for-

mation and elongation of the papillae of the proper plate of the esophageal mucosa [6, 7]. At this time, the stem cells of the basal layer at the height of the papillae are exposed to acid, enzymes and bile acids. In this regard, the basal epithelial progenitor cell, being pluripotent, can differentiate not into a flat, but into a cylindrical epithelium that is more resistant to the influence of refluxate components (a "defense mechanism" against the action of aggressive reflux factors).

There are other theories of the mechanism of Barrett's metaplasia development. One of the first hypotheses for the development of BE, which consisted of the ascending migration of gastric epithelial cells from the esophageal-gastric junction as a reparative mechanism for replacing damaged acid and other components of esophageal mucosa refluxate, has by now yielded to the point of view that PB de novo develops from cells inherent in the esophagus and not migrating from the stomach [4].

According to modern concepts, factors in the formation of a malignant neoplasm include the ability of carcinogenic agents to cause damage to the cell genome. Malignant progression of any localization is characterized by an increase in proliferation and a decrease in apoptosis [8]. The esophagus is no exception in this regard. Neoplastic progression occurs in patients with acquired genetic instability, in which pathological clones of cells appear, in which aneuploidy is determined, which allows us to consider aneuploidy in PB as a marker of a high risk of malignant progression [9].

The progression of BE also affects the barrier function of the esophageal epithelium. Dysregulation of the complex of molecules of E-cadherin and β-catenin, which are responsible for cell adhesion, and a decrease in their expression on the cell membrane occurs at the late stages of dysplasia development. In Barrett's esophagus, a decrease in the expression of E-cadherin and β-catenin is observed with an increase in dysplasia [10]. Moreover, the more the expression of these proteins is reduced, the worse the prognosis in EAC is.

With an increase in the expression of cyclooxygenase-2, cell adhesion decreases, angiogenesis and proliferation increase, and apoptosis decreases [11].

Another potential point of studying the progression of BE in EAC is the expression of a marker such as maspin. Research in this area has shown that lesions of each pathological grade can be divided into subtypes that show different patterns of the subcellular distribution of maspin, including nuclear only (Nuc), combined nuclear and cytoplasmic (Nuc + Cyt), only cytoplasmic (Cyt) and in general negligible (Neg). Thus, the Cyt subtype of the maspin expression pattern can serve as a molecular marker of early EAC [12].

According to the literary sources, studies of differentially expressed genes (DEG) are being conducted as potential markers of the "transition" of Barrett's esophagus to esophageal adenocarcinoma. Considering the results of some studies, it can be assumed that a panel of differentially expressed genes can occur in cases of high sensitivity to the effects of "risk factors" in the development of EAC, as well as in the progression of this pathological condition [5].

There is data on the study of p504s and CD133 markers, which can act as markers of proliferation and in the future will be used for the differential diagnosis of benign metaplasia and EAC [2].

Phosphorylated histone H3 is a potential marker by which it will be possible to differentiate between low- and high-grade dysplasia and EAC. According to the literary sources, adenocarcinoma had higher rates of mitosis (in terms of phosphorylated histone H3) than high-grade dysplasia [13].

Autophagy is of some importance in the pathogenesis of BE. Autophagy is a highly conserved mechanism that is activated during cellular stress. Presumably, autophagy can be caused by acid reflux, which causes damage and inflammation and, therefore, contributes to the development of BE and EAC [49]. Currently, the role of autophagy in BE and EAC is poorly understood. According to various researchers, autophagy functions to improve cell survival after refluxate damage. Thus, autophagy may play a decisive role in the pathogenesis and progression of BE, which requires further study [14, 15, 40].

Another important and actively studied area is the mechanism of epigenetic drift is a gradual change in the DNA methylation profile with the age of the organism [16]. Presumably, this is a consequence of dysregulation of the molecular apparatus that maintains the normal methylation profile, which consists of the attachment of a methyl group to the cytosine in the CpG dinucleotide at position C5 of the cytosine ring [16–18]. Methylation in the promoter region of a gene usually leads to suppression of transcription of the corresponding gene. Methylated cytosine, in turn, can then be oxidized by special enzymes, which leads to its demethylation back into cytosine. Knowing that EAC is, as a rule, a consequence of BE, where normal squamous cell epithelium is replaced by intestinal

epithelium in response to chronic gastroesophageal acid-biliary reflux, and both of these conditions are characterized by loss of heterozygosity, aneuploidy, specific genetic mutations and clonal diversity, genome and epigenomic analyses can increase the accuracy of risk stratification [17]. Tests for detecting molecular changes associated with tumor progression can be used to improve the pathological assessment of BE/EAC and to select patients at high risk of developing these pathologies for more intensive follow-up [16].

One should also consider that the development of BE and, in the future, EAC is associated with certain demographic and behavioral factors, including gender, obesity/increased body mass index (BMI) and smoking [17–19].

Thus, the pathogenesis of BE is currently not fully understood; it is most likely to be multifactorial. Because of the strong relationship between EAC and BE and between BE and GERD, factors involved in the development of GERD have been the focus of attention in recent years in an attempt to explain the observed increase in the prevalence of EAC. The processes of increased proliferation and suppression of apoptosis, damage to the factors of the barrier function of the epithelium play an important role in the pathogenesis of BE and its progression into EAC.

According to the data we have analyzed, the following markers are most often used to diagnose and assess the prognosis in BE and EAC:

– Ki 67 protein expression,

– p53 gene mutation,

– BE aneuploidy,

– increased expression of COX-2 (low specificity, actively studied as a marker involved in the pathogenesis of PB),

– VEGFR (a marker of angiogenesis).

Table 1 summarizes the characteristics of some of the molecular markers.

Table 1

Markers of Barrett's Esophagus and Esophageal Adenocarcinoma	
Proliferation markers	***MUC-1*** "Intestinal" mucin. Its diagnostic sensitivity in BE is 95%. In 55% of cases, it is found in goblet cells. With severe dysplasia, i.e. progression of BE, its expression in cells increases [20].
	Ki-67 It is a classic marker of cell proliferation. Its expression makes it possible to isolate cells that are in the active phase of the cell cycle throughout its entire length (G1-, S-, G2- and M-phases). Ki-67 is absent only in the G0-period. If Ki-67 is less than 15%, the tumor is considered less aggressive; if it is more than 30%, the tumor is considered highly aggressive [21.22].
	CCK2R Cholecystokinin-2 (CCK2R) receptors are overexpressed in various malignant diseases and therefore attract some attention as potential markers for studying the progression of Barrett's esophagus into EAC [24].
	TFF1, TFF2 Trefoil factors are found in the secretions of goblet cells and Paneth cells and provide regulation of proliferation, differentiation and apoptosis [24].
	SATB1 SATB1 influences the expression of hundreds of genes, including some that are involved in the pathogenesis of human cancer. These data suggest that SATB1 may be involved in carcinogenesis and/or progression of human malignant tumors. SATB1 shows promise as a prognostic biomarker and a novel therapeutic target based on its expression level in solid tumors [25–27].
	Mcm2 Minichromosome maintenance protein is involved in all stages of cellular cycle. Representation in adenocarcinoma is 28.4% to 3.4% in non-progressive forms [28].
	P53 In the presence of mutations, accumulation occurs, including that in the nucleus of cells. The presence of the marker varies from 5% (no dysplasia); 10–20% for low-grade dysplasia, over 60% for high-grade dysplasia, and over 70% for adenocarcinoma [29, 30].
	PCNA (Proliferating cell nuclear antigen) is a nuclear non-histone protein required for DNA synthesis. It is an auxiliary protein for DNA polymerase alpha, which increases during the G1/S phase of the cell cycle. Expression of PCNA can be used as a marker of cell proliferation since cells proliferate for a longer time in the G1/S phase. In addition, this protein plays an important role in the metabolism of nucleic acids as a component of the mechanism of DNA replication and repair [10].
	P27 Inhibits the E/Cdk2 complex, which prevents the onset of the S stage of the cell cycle. The main types of damage are hypermethylation, decreased heterozygosity [28].

Table (continued)

Proliferation markers	***TGFα*** They stimulate VEGF secretion by acting on metaplastic PB cells [31].
	EGFR EGFR is an oncogene that encodes a transmembrane tyrosine kinase receptor. Its dysregulation has been linked to several types of human cancers [31].
	TGFβ It is central in the epithelial homeostasis, regulating both proliferation and differentiation. In normal cells, one of the functions of TGFβ is to induce cell-cycle block, and many epithelial tumors are resistant to this response. In contrast, TGFβ is involved in the epithelial-mesenchymal transition in tumor cells, especially at invasive margins, where this change in phenotype is believed to promote invasion and metastasis. Expression of TGFβ is increased in EAC compared to the normal esophagus and BE [31].
	erbB-2/Her2 receptor is amplified in approximately 10-50% of esophageal adenocarcinoma, with concomitant overexpression of mRNA or protein. Presumably, this lesion is a late stage in the carcinogenesis of Barrett's esophagus [31].
	Cyclooxygenase-2 (COX-2) is a key enzyme in the prostaglandin synthesis pathway. It is believed that chronic inflammation can stimulate tumor development, at least in part due to mediators such as prostaglandins, which suggests that COX-2 promotes carcinogenesis in BE. Increased expression of COX-2 is found during the progression from BE to EAC and is associated with proliferation and decreased survival [30, 31].
	MicroRNA **MicroRNA (miRNAs), a** class of endogenous and single-stranded RNA, is a subfamily of small non-coding regulatory RNA, 18–22 nt in size, involved in various physiological and pathological processes. miRNAs play an important role in oncogenesis by directly or indirectly regulating the expression of various oncogenes or tumor suppressors [32].
	CYFRA 21-1 One of the structural elements of epithelial cells, which forms their framework (cytoskeleton), and numerous cytokeratin proteins. There are about 25 types of proteins, and Cyfra 21-1 is used to diagnose some cancerous tumors [33].
	Fibronectin 1 Fibronectin 1 (FN1) is a member of the glycoprotein family located on the 2q35 chromosome. It has been reported that FN1 is activated in many tumors, and its expression is negatively associated with the prognosis and survival of cancer patients [34].
	Leptin It has been demonstrated that the expression of leptin and its receptor is present in cell cultures of some types of esophageal cancer, and the addition of recombinant leptin to these cell lines leads to a significant dose-dependent increase in cell proliferation and suppression of apoptosis [35].
	P21 The exact role of p21 in carcinogenesis has not yet been fully established. Studies show that in some types of tumors, loss of p21 is a sign of a poor chance of survival. However, situations are known when an increased concentration of this protein in cells positively correlates with the aggressiveness of the tumor and its ability to metastasize. This is particularly the case when p21 accumulates in the cytoplasm, and not in the cell nucleus [22, 31].
	CDX2 The cdx2 gene encodes a specific transcription factor; its protein is expressed in the early stages of small intestine development and may be important in the regulation of proliferation and differentiation of small intestinal epithelial cells. It is expressed in the nuclei of intestinal epithelial cells from the duodenum to the rectum. The protein is expressed in primary and metastatic tumors of the large intestine and is detected in intestinal metaplasia of the stomach and intestinal type of gastric cancer. It is not found in normal epithelial cells of the stomach [28, 36].
Markers of angiogenesis	***VEGF, VEGFR*** Provide neorevascularization of metaplastic tissues which is one of the early events supporting the tumor progression of BE [37].
	VEGFR -1,2 VEGFR-1 regulates angiogenesis through mechanisms that include ligand uptake, homo- and heterodimerization of receptors. Its function in angiogenesis may include its ligand-binding extracellular region, acting as a VEGF trap to modulate the function of VEGFR-2 (which in turn is a receptor for vascular endothelial growth). The study of these markers plays an important role in the creation of "compounds" aimed at suppressing vascular growth in tumors [37].
Markers of apoptosis	***P16*** The main types of damage are hypermethylation, decreased heterozygosity, mutations, and promotor methylation. A decrease in heterozyosity is observed in 75% of patients with adenocarcinoma [31].
	NF-kb (Nuclear Factor kappa B) is activated in various types of cancer. This mediator of carcinogenesis forces malignant tumor cells to avoid apoptosis from the checkpoint of the cell cycle. In recent years, many studies have been performed demonstrating that miRNAs and NF-κB play an important role in the development and progression of tumors [34].

Table (continued)

Markers of autophagy	**mTORC1 complex** regulates the signaling pathway leading to the activation of autophagy by phosphorylation and inhibition of the kinase activity of ULK1 (Unc-51-like kinase 1). After nutrient deprivation, mTORC1 repression is attenuated, and active ULK1 forms a complex with mAtg13, FIP200 (or RB1CC1), and Atg101, which leads to activation of autophagy [38].
	UV Radiation Resistance Associated Gene (UVRAG) is a tumor suppressor involved in autophagy. UVRAG, originally identified as a BECN1-binding macroautophagy/autophagy protein, UVRAG directs a variety of cellular processes to maintain homeostasis and genetic stability, including ER-Golgi transport, endosomal degradation, DNA repair, and centrosome integrity. Consequently, tumor cells may "seek to inactivate" UVRAG in some contexts to remove an important barrier to cancer development [15, 39, 45].
	ATG is a gene associated with autophagy. ATG8 protein is involved in autophagosome formation, load recognition, and recruitment to autophagosomes. At least seven homologues of ATG8 (mammalian ATG8, mATG8) are expressed in human cells. They are usually divided into two subfamilies of GABARAP (Gamma-aminobutyric acid receptor-associated protein A) proteins, including GABARAP / -L1 / -L2, as well as LC3, which includes LC3A (a, b) / B / C [14, 41−43].
	ULK1 is recruited into the Beclin-1-ATG14L-VPS34 complex through its interaction with ATG14L. Beclin-1 is activated by the phosphorylation of ULK1, and, therefore, the PI3 activity of the VPS34 kinase stimulates the production of PtdIns P, which is necessary for the formation and/or maturation of autophagosomes [37,38, 40].
	Lipid kinase VPS34 is an important mediator of many aspects of intracellular transport through the formation of phosphoinositide-3-phosphate (PI (3) P) on membranes [40, 44].

Based on the analysis of the literature available to us, it was revealed that studies in the field of etiology, the pathogenesis of BE and EAC, as well as verification of these pathological conditions, prognosis and choice of treatment methods, remain incomplete. There is a situation of untimely detection and, accordingly, late initiation of BE treatment, in connection with which the risk of EAC development increases. The literature analyzed shows a rather high risk of developing EAC against the background of BE which opens up new opportunities for us in the diagnosis and treatment of these pathological conditions. From our point of view, the most urgent are the issues of a detailed study of the markers of proliferation, apoptosis, autophagy and angiogenesis, the selection of the most significant of them for the early diagnosis of esophageal pathology and the use of markers as a possible immunobiological therapy for Barrett's esophagus and esophageal adenocarcinoma. Consequently, the study of this problem does not lose its relevance and requires further research.

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Received 25.10.2019
Accepted 30.04.2020